Impacts des médicaments écrasés sur le goût et sur le biofilm oral

Julie Lamure

UNIVERSITE NICE-SOPHIA ANTIPOLIS

Ecole Doctorale des Sciences de la Vie et de la Santé

THESE
pour obtenir le titre de

Docteur en Sciences
de l'UNIVERSITE NICE SOPHIA-ANTIPOLIS

Discipline : Immunologie et Microbiologie

Présentée et soutenue par

Julie Lamure

Impacts des médicaments écrasés sur le goût et sur le biofilm oral

Thèse dirigée par le Pr Isabelle PRECHEUR

Soutenue le 30 novembre 2015

Jury:	Pr Virginie MONNET-CORTI	Présidente du Jury
	Pr Alain PESCE	Rapporteur
	Pr Isabelle PRECHEUR	Directrice de thèse
	Dr Alain DOGLIO	Examinateur

SOMMAIRE

REMERCIEMENTS

A Madame la Professeur Isabelle Virginie MONNET-CORTI

Docteur en Chirurgie Dentaire
Docteur de l'Université d'Aix Marseille
Professeur des Universités - Praticien Hospitalier
Responsable de la sous-section de parodontologie
Faculté d'odontologie – Université Aix Marseille

Vous me faites un très grand honneur en présidant ce jury de thèse.
Je vous remercie d'avoir accepté de juger ce travail et d'en être le rapporteur
Veuillez trouver, dans ce travail le témoignage de toute ma gratitude et de mon profond respect.

A Monsieur le Professeur Alain PESCE

Docteur en Médecine
Professeur des Universités - Praticien Hospitalier
Département de Gérontologie Clinique et Mémoire - Centre Rainier III
Centre Hospitalier Princesse Grace – Principauté de Monaco
Centre de Coordination Gérontologique – Principauté de Monaco

Je vous remercie pour l'intérêt que vous portez à ma thèse en acceptant de juger ce travail et d'en être le rapporteur.
Veuillez trouver, dans ce travail le témoignage de toute ma gratitude

A Madame la Professeur Isabelle PRECHEUR

Docteur en Chirurgie Dentaire
Docteur de l'Université de Nice Sophia Antipolis
Professeur des Universités - Praticien Hospitalier
Faculté d'odontologie – Université de Nice Sophia-Antipolis

Je vous remercie d'avoir dirigé mes travaux de recherche mais également de m'avoir accordé votre aide et votre temps pour ce travail.
Pour la qualité de votre enseignement je vous prie de bien vouloir trouver ici,
L'expression de mon profond respect

A Monsieur le Docteur Alain DOGLIO

Docteur en Sciences
Docteur de l'Université de Nice Sophia Antipolis
Maître de Conférences des Universités - Praticien Hospitalier
Responsable Unité de Thérapie Cellulaire et Génique (UTCG, CHU de Nice)
Directeur Laboratoire Microbiologie Orale, Immunothérapie et Santé (MICORALIS EA7354, UNS)

Je vous remercie d'avoir accepté de siéger dans ce jury
J'ai pu apprécier votre disponibilité, compétence, et gentillesse au sein du laboratoire.
Veuillez trouver dans ce travaille témoignage de mon profond respect

INTRODUCTION

Démographie : Le vieillissement de la population

Au premier janvier 2015, la France comptait 11,9 millions de personnes âgées de plus de 65 ans. Les personnes de plus de 60 ans représentent 20% de la population française. L'espérance de vie ne cesse d'augmenter. En 2015, elle est de 79,2 ans pour les hommes et 85,4 ans pour les femmes. En 2010, 15000 centenaires vivaient en France, soit treize fois plus qu'en 1970. Si les tendances démographiques persistent, la population des plus de 60 ans augmentera de 10,4 millions entre 2007 et 2060. Cela signifie qu'une personne sur trois sera âgée de plus de 60 ans en 2060. [1] L'espérance de vie en bonne santé progresse par contre plus lentement. Elle est de 62,6 années pour les hommes et 63,8 années pour les femmes. On aura donc une population plus âgée mais dépendante. En 2012 le nombre de personnes âgées dépendantes représentait 1,13 millions [2].

EHPAD, dysphagie, anorexie et médicaments écrasés

Les personnes âgées dépendantes vivent à leur domicile si la présence d'un ou plusieurs aidants dans l'entourage le permet. Mais la majorité des personnes âgées dépendantes résident en EHPAD (établissement d'hébergement pour personnes âgées dépendantes). Cela correspond aux maisons de retraite médicalisées. Les EHPAD peuvent accueillir des personnes âgées très dépendantes. Ces résidents souffrent de maladies chroniques et ils sont souvent polymédiqués. Le personnel soignant leur administre en moyenne 6 à 8 médicaments par jour ce qui représente 6 à 20 comprimés ou gélules par jour. Certains patients hébergés en EHPAD souffrent de problème de déglutition ("fausses routes" ou dysphagies). La prévalence de la dysphagie augmente avec l'âge. Au moins 15% de la population âgée et jusqu'à 50% des résidents d'EHPAD souffrent de dysphagie à cause de la maladie de Parkinson, d'un accident vasculaire cérébral, de la maladie d'Alzheimer ou d'une sécheresse buccale (syndrome de Gougerot-Sjögren, sécheresse buccale d'origine médicamenteuse). La dysphagie augmente le risque de pneumonie d'aspiration, par inhalation de salive contaminée par les bactéries buccales dans les voies respiratoires. Le refus de s'alimenter qui en résulte peut entrainer déshydratation, une anorexie et la mort. Les médicaments sont souvent écrasés et mélangés dans

une compote ou un laitage, pour pouvoir être pris par les personnes âgées qui ont des troubles de la déglutition ou des troubles du comportement [2]. Les alternatives (voie parentérale, sonde gastrique) sont plus agressives et limitées aux situations aiguës ou transitoires. Une étude prospective a été menée auprès de 683 malades hospitalisés dans toutes les unités de Gériatrie du CHU de Rouen en 2009 [3]. Les médicaments étaient écrasés pour 32,3% des patients, principalement à cause de troubles de la déglutition (67,1%) ou de troubles du comportement (27,5%). La Haute Autorité de Santé a publié une liste des médicaments autorisés à être écrasés, car cette pratique peut modifier la pharmacocinétique de certains médicaments, et les rendre inactifs voire toxiques [4]. En pratique la réalité est différente : 41,5% des comprimés ou gélules administrés après écrasement avaient une forme galénique interdisant l'écrasement [3].

Après 70 ans, la dénutrition protéino-énergétique est définie par une perte de poids > 5% en 1 mois ou > 10% en 6 mois, une diminution de la masse corporelle totale, en particulier aux dépens de la masse musculaire, un indice de masse corporelle (IMC) < 21 [5]. La dénutrition est fréquente en gériatrie et sa prévalence augmente avec l'âge. Chez les personnes âgées de plus de 70 ans, elle varie de 4% à 25-30% à domicile en cas de perte d'autonomie. Elle atteint 15-38% en institution et 50-60% à l'hôpital [5]. Les polypathologies et la polymédication favorisent la dénutrition protéino-énergétique [5, 6]. Au niveau buccal , les altérations bucco-dentaires et les altérations du goût augmentent le risque de dénutrition [7]. En bouche, la diminution du coefficient masticatoire, la sécheresse buccale et les douleurs buccales sont des facteurs de risque indépendant de dénutrition [7–10].

Le goût

Après 75 ans, le nombre de papilles gustatives diminue et celles qui demeurent s'appauvrissent en bourgeons du goût. À cet âge, la perception des sensations de base est amoindrie mais le goût du sucré est mieux préservé. Le goût fait partie des facteurs de régulation de l'appétit. Il joue donc un rôle dans l'anorexie des personnes âgées en diminuant le plaisir de manger [11]. Outre le

vieillissement naturel des sens, les médicaments peuvent avoir un effet indésirable intrinsèque sur le goût. Certains médicaments écrasés pourraient modifier le goût des aliments dans lesquels ils sont mélangés.

Biofilm Oral

Comme toutes les surfaces orales, le pôle externe des bougeons du goût est isolé du milieu buccal par un biofilm microbien endogène. Les molécules sapides ont l'aptitude de traverser les micro-canaux qui traversent le biofilm sain pour accéder aux bourgeons du goût. Plus de 700 espèces bactériennes ont été identifiées dans le biofilm oral [12]. Ces bactéries ont un potentiel d'adhésion sur toutes les surfaces dentaires, muqueuses et sur les prothèses et matériaux de restaurations dentaires. Ces bactéries s'organisent en une structure tri-dimensionnelle [13] [14] [15], intégrées dans une matrice exo-polysaccharide [16]. Le biofilm oral est souvent colonisé par des champignons inférieurs du genre *Candida*, en particulier *Candida albicans*. Certaines bactéries sont impliquées dans les maladies orales comme les parodonties et les caries dentaires. Ce sont les infections bactériennes les plus fréquentes chez l'homme. Par exemple 53,1% des américains âgés de 30 à 90 ans ont une perte d'attache parodontale supérieure ou égale à 3 mm [17]. Il est très fréquent d'étudier des bactéries spécifiques d'une pathologie. Mais le biofilm sain a souvent été négligé [18]. La communauté microbienne varie entre différents sites de la cavité buccale (dent, palais, langue, tissus mous …) [19]. La plupart des genres bactériens oraux sont communs à tous les sites oraux, par exemple *Gemella, Granulicatella*, *Streptococcus* et *Veillonella*. Chaque site oral présente 20 à 30 espèces prédominantes. Les différents sites oraux dans leur globalité possèdent 34 à 72 espèces prédominantes par individu sain [18].

Les principes actifs ou l'enrobage des médicaments pourraient avoir un impact sur les bactéries et les *Candida* du biofilm oral, lorsqu'ils sont directement à leur contact.

Sécheresse buccale

Les bactéries orales endogènes assurent l'hydratation et la viscosité du biofilm oral, et elles sont indispensables à une bouche saine et au confort du patient. Au contraire, un biofilm oral altéré peut se traduire par une bouche sèche. La xérostomie est une sensation subjective de sécheresse buccale et l'hyposalivation est une diminution objective du volume de sécrétion salivaire. Face à l'absence de consensus dans le traitement de la sécheresse buccale, il paraît nécessaire de combattre les facteurs iatrogènes [20]. L'utilisation de bains de bouche antiseptiques pendant plus de deux semaines déséquilibre le biofilm oral. Les principes actifs antiseptiques couramment utilisés dans les bains de bouche sont la chlorhexidine et l'hexétidine, le triclosan. Les huiles essentielles et l'alcool sont souvent utilisés comme adjuvants, mais ils ont aussi des propriétés antiseptiques. La pratique des médicaments écrasés pourrait aussi contribuer à expliquer la sécheresse buccale, qui est très fréquente chez les résidents des EHPAD. La sécheresse buccale augmente notamment le risque de candidoses orales, de pneumonies d'inhalation, d'anorexie et de dénutrition.

Objectifs de la thèse

Nous avons d'abord étudié l'impact des bains de bouche antiseptiques, qui altèrent le biofilm oral, sur la xérostomie. Nous avons ensuite testé les 30 médicaments les plus souvent prescrits dans les 596 EHPAD du groupe Korian, dont la liste complète nous a été transmise par la direction médicale du groupe.

Le 1er objectif était de déterminer l'impact des médicaments écrasés sur le goût de volontaires sains, afin de déterminer quels médicaments étaient acceptables ou à déconseiller dans les aliments (étude sur les 10 médicaments les plus prescrits).

Le 2ème objectif était de rechercher in vitro si certains médicaments écrasés pouvaient inhiber ou au contraire stimuler la croissance microbienne et risquaient d'altérer le biofilm oral.

Annexe :

Liste des 30 médicaments les plus prescrits dans les EHPAD du groupe Korian, par ordre décroissant de fréquence de prescription

Principe actif	Médicament écrasable
Paracétamol	E
Acide acétylsalicylique	
Furosémide	E
Lévothyroxine sodique	E
Mémantine	E
Chlorure de potassium (E508)	
Zopiclone	E
Amlodipine	
Alprazolam	E
Oxazépam	E
Rispéridone	
Miansérine	
Donépézil	E
Macrogol 4000	
Clopidogrel	E
Carbonate de calcium (E170) ; cholécalciférol	
Bensérazide;Lévodopa	
Ramipril	E
Acide folique	E
Amiodarone	E
Rivastigmine	
Glycérol (E422) ; paraffine ; vaseline	

CHAPITRE I

Antiseptic mouthwashes could worsen xerostomia in patients taking polypharmacy

Chevalier M, Sakarovitch C, Precheur I, Lamure J, Pouyssegur-Rougier V

Published in

Acta Odontologica Scandinavica

Taylor & Francis

May 2015; 73(4):267-73.

DOI: 10.3109/00016357.2014.923108. Epub 2015 Jan 20

CHAPITRE I – Avant propos

Résumé

Objectifs : La polymédication est une cause fréquente de xérostomie. Cette étude a pour objectif d'étudier si la xérostomie serait un effet indésirable des bains de bouche, lorsqu'ils sont utilisés pendant plus de deux semaines chez des patients polymédiqués.

Matériels et Méthodes : Cette étude observationnelle inclus 120 patients hospitalisés (60 d'âge moyen et 60 personnes âgées) polymédiqués (> 4 médicaments par jour) et à risque de xérostomie médicamenteuse. La xérostomie est évaluée en questionnant les patients.

Résultats : 62.5% des patients se plaignent de xérostomie. Dans le groupe d'âge moyen, la xérostomie semblerait indépendamment associé à l'utilisation des bains de bouche (OR = 5.00, 95% CI = 0.99-25.3, *p*= 0.052). Les principes actifs des bains de bouche sont principalement des composants d'ammonium quaternaire (chlorhexidine, hexétidine, chlorure cetylpyridinium). Les bains de bouche perturberaient l'équilibre sain du biofilm humidifiant la muqueuse orale. Le biofilm contient des mucines, des glycoprotéines salivaires avec des oligosaccharides capables de séquestrer l'eau et les bactéries endogènes entourés par un glycocalyx. Les bactéries orales sont hautement sensibles aux ammoniums quaternaires et aux autres antiseptiques utilisés dans les bains de bouche comme la povidone iodée, le triclosan, les huiles essentielles, l'alcool et la résorcine. Cependant, les professionnelles de santé recommandent fréquemment ces produits pour le contrôle de plaque, chez les patients souffrant de xérostomie, pour diminuer les risques de caries et de parodontites.

Conclusion : Cette étude est le première démontrant que les bains de bouche utilisés plus de deux semaines pourraient empirer la xérostomie chez les patients polymédiqués.

Acta Odontologica Scandinavica
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/iode20

Antiseptic mouthwashes could worsen xerostomia in patients taking polypharmacy

Marlene Chevalier[ab], Charlotte Sakarovitch[c], Isabelle Precheur[ad], Julie Lamure[ad] & Valerie Pouyssegur-Rougier[ad]

[a] [1]Laboratory of Oral Health and Aging, Faculty of Dentistry, University Nice Sophia Antipolis, Nice, France

[b] [2]IP-TPT UMR MD3, Aix-Marseille University, Marseille, France

[c] [3]Department of Clinical Research, Nice University Hospital, Nice, France

[d] [4]Department of Dentistry, Nice University Hospital, Nice, France

Published online: 20 Jan 2015.

To cite this article: Marlene Chevalier, Charlotte Sakarovitch, Isabelle Precheur, Julie Lamure & Valerie Pouyssegur-Rougier (2015) Antiseptic mouthwashes could worsen xerostomia in patients taking polypharmacy, Acta Odontologica Scandinavica, 73:4, 267-273

To link to this article: http://dx.doi.org/10.3109/00016357.2014.923108

Acta Odontologica Scandinavica. 2015; 73: 267–273

informa
healthcare

ORIGINAL ARTICLE

Antiseptic mouthwashes could worsen xerostomia in patients taking polypharmacy

MARLENE CHEVALIER[1,2], CHARLOTTE SAKAROVITCH[3], ISABELLE PRECHEUR[1,4], JULIE LAMURE[1,4] & VALERIE POUYSSEGUR-ROUGIER[1,4]

[1]*Laboratory of Oral Health and Aging, Faculty of Dentistry, University Nice Sophia Antipolis, Nice, France,* [2]*IP-TPT UMR MD3, Aix-Marseille University, Marseille, France,* [3]*Department of Clinical Research, Nice University Hospital, Nice, France, and* [4]*Department of Dentistry, Nice University Hospital, Nice, France*

Abstract

Objective. Polypharmacy is a common cause of xerostomia. This study aimed to investigate whether xerostomia could be an adverse drug event of mouthwashes, when they are used for longer than 2 weeks by patients taking polypharmacy. ***Materials and methods.*** This cross-sectional observational study included 120 hospitalized patients (60 middle-aged and 60 elderly patients), taking polypharmacy (≥4 drugs daily) and at risk of drug-induced xerostomia. Xerostomia was assessed by questioning participants. ***Results.*** A total of 62.5% of patients complained of xerostomia. In the middle-aged group (mean age = 44.0 (8.7) years; 35.0% women) xerostomia seemed independently associated to mouthwashes, at the limit of significance (OR = 5.00, 95% CI = 0.99–25.3, $p = 0.052$). Active principles in mouthwashes were mainly quaternary ammonium compounds (91.9%). Mouthwashes may disturb the healthy balance of the biofilm moisturizing the oral mucosa. The biofilm contains mucins, salivary glycoproteins with oligosaccharides side chains able to sequester water and endogenous bacteria surrounded by a glycocalyx. Oral bacteria are fully susceptible to quaternary ammonium (chlorhexidine, hexetidine, cetylpyridinium chloride) and to other antiseptics used in mouthwashes, such as betain, resorcin, triclosan, essential oils and alcohol. However, caregivers currently recommend such dental plaque control products to patients suffering from xerostomia in order to reduce the risk of caries and periodontitis. ***Conclusion.*** This study is the first report that use of antiseptic mouthwashes for more than 2 weeks could worsen xerostomia in patients taking polypharmacy. Oral care protocols should avoid this iatrogenic practice, particularly when xerostomia alters the quality-of-life and worsens malnutrition.

Key Words: *adverse drug event, biofilm, iatrogenic disease, xerostomia*

Introduction

Alterations of saliva physiology include xerostomia, hyposalivation and altered saliva composition. Xerostomia is a subjective feeling of oral dryness. Mouth dryness is a term regarding dryness in the oral cavity, objectively diagnosed by for instance a dental mouth mirror sticking to the buccal mucosa of the cheek due to dryness. Xerostomia varies substantially between individuals [1,2]. According to Glore et al. [3], dry mouth is not necessarily related to decreased salivary flow. Some patients experience a feeling of oral dryness, despite seemingly normal, objectively measured levels of saliva secretion [4], whereas others do not complain about dry mouth, despite objectively diagnosed hyposalivation [5]. However, most individuals experience a sensation of oral dryness when their salivary output is less than about half of the normal output in health, but with great variation [2].

The prevalence of xerostomia reaches 10–20% in the general population, primarily in women, and 50% in the elderly [1,6]. Symptoms of mouth dryness include a sensation of thirst, soreness and dryness of the lips and oral mucosa [7,8]. It is associated with an increased risk of caries, oral candidiasis, removable denture intolerance, taste disturbance and pneumonia, with a subsequent risk of eating difficulties,

Correspondence: Marlene Chevalier, Laboratory of Oral Health and Aging, Faculty of Dentistry, University Nice Sophia Antipolis, 06357 Nice cedex 4, France. Tel: +33 4 92 00 11 25. Fax: +33 4 92 00 12 63. E-mail: marlene.chevalier@unice.fr

(Received 31 October 2013; accepted 15 April 2014)

ISSN 0001-6357 print/ISSN 1502-3850 online © 2015 Informa Healthcare
DOI: 10.3109/00016357.2014.923108

choking, loss of appetite and malnutrition [6,8–10]. Treatment protocols may include: general and local hydration, saliva substitutes and lubricants, central (pilocarpine, cevimeline) and local (sugar-free chewing-gums and candies) secretagogues, antifungal treatment, topical analgesics before meals, suppression or replacement of xerogenic drugs, dietary modification and/or dietary supplements and oral hygiene reinforced with antiseptic oral care products. No treatment or combination treatment is fully satisfactory in combating xerostomia [1,2,11–13].

Common causes of xerostomia include dehydration, autoimmune (Sjögren's syndrome) and endocrine (diabetes) diseases, hepatitis C virus (HCV) infection and radiation therapy of head and neck tumors [12,14,15]. Many commonly prescribed medications are associated with the feeling of mouth dryness, despite normal saliva production [1,2]. In the elderly, the main cause of xerostomia is medication and, in particular, the use of ≥4–5 drugs per day [2]. More than 500 medications are associated with xerostomia, with special emphasis placed on psychotropic drugs (anticholinergic drugs/atropinics, neuroleptics, tricyclic antidepressants, antipsychotics, benzodiazepines), followed by anti-hypertensives, diuretics, anti-neoplastics, opiates, bronchodilatators, proton pump inhibitors, antihistamines and others [6–9,16,17]. However, few medications except for true anticholinergic drugs have been demonstrated to affect salivary function and polypharmacy remains the most prevalent cause of mouth dryness [4,14,16]. Actually, xerostomia is not listed either among indications of antiseptic mouthwashes or among their side-effects. However, we observed that, in all the previous series investigating polypharmacy and xerostomia, no attention had ever been paid to topical medications such as antiseptic mouthwashes [2,16,17].

Antiseptic mouthwashes are efficient against bacterial species colonizing the oral biofilm and their use must not exceed 2 weeks [18]. However, misuse of antiseptic mouthwashes for longer than a 2-week period is frequently reported by patients, with the risk to unbalance the oral bacterial biofilm coating oral mucosa. Besides, the biofilm contains salivary and bacterial glycoproteins, the primary function of which are to retain water [19].

Due to the absence of consensual treatment for xerostomia [2,6], it might be necessary to combat iatrogenic factors. We hypothesized that, in addition to low saliva secretion induced by systemic drugs, mouth dryness could be worsened by biofilm alterations induced by local antimicrobial medications.

The objective of the present work was to investigate the link between xerostomia and the use of antiseptic mouthwashes for a duration of time longer than 2 weeks, in patients taking polypharmacy.

Materials and methods

Study design and patients

This cross-sectional observational study included 120 patients from Nice University Hospital: 60 middle-aged patients (Mean age = 44 (8.7)) from the Department of Infectious Diseases and 60 elderly patients (Mean age = 84.5 (8.0)) from the Department of Geriatrics. Patients recruited in the Infectious Diseases Department suffered mainly from human immunodeficiency virus (HIV) infection or HCV chronic hepatitis. Patients recruited in the Geriatrics Department suffered from various cardiovascular, endocrine, psychiatric and other chronic disorders. Both of these populations had a high probability to be given polypharmacy. Such patients frequently complained of xerostomia and exhibited mucosal dryness. We enrolled consecutive patients seen at the Department of Dentistry for routine dental examination. All participants taking four drugs or more daily were eligible for the study and there was no exclusion criterion. All participants gave written informed consent. The study was approved by the Clinical Research Department of Nice University Hospital and by the local Ethics Committee (May 6, 2013; registration number 20100108).

Data collection

The main variable was subjective xerostomia. According to the protocol described by Thomson et al. [20], participants were asked the question 'How often does your mouth fell dry?' with four possible answers: 'Always', 'Frequently', 'Occasionally' or 'Never'. Patients who answered 'Always' or 'Frequently' were considered as suffering from xerostomia.

Other data were obtained from patient interviews, routine dental examinations and hospital medical files. Collected data includes gender, age and common known associations with xerostomia: Sjögren's disease, dehydration, head and neck radiation therapy, tobacco use, previous or current illicit drug addiction, HIV or HCV infection, depressive disorders, diabetes mellitus, Parkinson's disease, number of drugs taken per day and loss of appetite. Recent non-voluntary weight loss and body mass index (BMI: [mass in kg]/[height in m]^2) were also noted. Xerostomia and use of antiseptic mouthwashes for longer than 2 weeks duration were recorded. Routine oral parameters were charted: oral candidiasis (denture stomatitis, acute stomatitis, erythematous stomatitis), oral pain, oral ulcerations, active dental caries, edentulousness, removable denture(s) and masticatory ability [21].

Patients' medications were also recorded. Each psychotropic agent was categorized as follows: muscarinic antagonists (true anticholinergic/atropinic

drugs), adrenergic alpha-antagonists, opioid agonists, serotonin 5-HT2 blockers, histamine H1 antagonists, dopamine D2 receptors blockers or GABA-A receptor agonists. Some were classified in more than one category; for instance, risperidone is a selective blocker of dopamine D2 receptors and serotonin 5-HT2 receptors and it was attributed to both categories. Other drugs were charted as follows: paracetamol, glucocorticoids, antibacterial agents, antifungal agents, anti-HIV agents, diuretics, adrenergic beta-blockers, angiotensin-converting enzyme inhibitors, sodium potassium pump inhibitors, iron supplements, calcium channel blockers, platelet aggregation inhibitors, coumarin anticoagulants, heparin, proton pump inhibitors, anti-diabetic agents, etc.

Data analysis

Analysis was performed separately for the middle-aged patients group and for the elderly patients group, using SAS statistical package, version 9.1.3 (SAS Institute, Inc., Cary, NC). In univariate analysis, the association between xerostomia and quantitative parameters were assessed using Student's *t*-test or Wilcoxon test if Student's *t*-test hypothesis was not verified. Association between xerostomia and qualitative variables were assessed using the chi-square test or Fisher's exact test in case of small expected frequencies.

Multivariate analysis was performed using logistic regression. The analysis was adjusted on risk factors known to be associated with xerostomia ('woman', 'number of drugs taken per day' and 'use of psychotropic drugs') [1,2]. In addition, the variables associated with $p < 0.1$ in the univariate analysis were included in the multivariate model. Statistical significance was accepted at 5% ($p \leq 0.05$).

Results

Patients of both groups were heavily medicated with up to 18 drugs per day. Seventy-five out of the 120 patients (62.5%) suffered from subjective xerostomia and 37 patients (30.8%) reported regular use of antiseptic mouthwashes. They used them once or more daily at home for more than 2 months and they continued this habit during their hospitalization. Most of the antiseptic mouthwashes contained quaternary ammonium compounds (34/37: 91.9%): chlorhexidine gluconate (n = 19, combined with chlorobutanol, alcohol and levomenthol), hexetidine (n = 12, combined with alcohol and menthol), cetylpyridinium chloride (n = 3, combined with chlorobutanol, eugenol, menthol and castor oil). Other mouthwashes contained sodium bicarbonate (n = 1), alcohol and anethole combined with other essential oils (mint, cinnamon, clove and benzoin) (n = 1) and salicylic acid combined with alcohol, levomenthol, resorcinol and veratrol (n = 1). No patient reported the use of antimicrobial oral care products specifically designed for daily oral hygiene. For the inclusive patients, no element in favour of dehydration at the clinical or biological level was noted in the medical record. In this study, we observed only denture stomatitis and no acute or erythematous stomatitis. However, we did not make an oral sample in search of *Candida*.

The two groups of patients are described in Tables I and II. In the group of middle-aged patients, risks factors for xerostomia were as follows: younger age (42.5 (9.4) years vs 46.5 (6.9) years; $p = 0.08$), woman (46.0% vs 17.4%; p = 0.024), use of antiseptic mouthwashes for a duration of time longer than 2 weeks (43.2% vs 17.4%; p = 0.039), tobacco use (83.8% vs 60.9%; p = 0.046) and use of GABA treatment (43.2% vs 17.4%; $p = 0.039$). In the group of elderly patients, risks factors for xerostomia were as follows: number of drugs taken per day (9.0 (2.9) vs 6.6 (3.2); $p = 0.005$), use of sodium potassium pump inhibitors (36.4% vs 13.6%; p = 0.055) and use of psychotropic drugs (57.9% vs 22.7%; p = 0.008).

In the group of middle-aged patients, multivariate analysis showed an association between xerostomia and the variable 'use of antiseptic mouthwashes', at the limit of significance (adjusted odds ratio (OR) = 5.00, 95% CI = 0.99–25.3; p = 0.052) (Table III). However, in the group of elderly patients, the association between xerostomia and the variable 'use of antiseptic mouthwashes' was not statistically significant (OR = 1.70, 95% CI = 0.44–6.62; $p = 0.44$).

In the younger population, the multivariate model included, in addition to the forced variables cited above, the variable 'age' (year), 'tobacco use' (yes/no) and 'use of GABA treatment' (yes/no). The variable 'use of GABA treatment' was no longer associated to xerostomia after adjustment (p = 0.53) and did not modify the association between 'use of antiseptic mouthwashes' and xerostomia, therefore the variable was removed from the final model. As previously described, we observed in younger patients an association between xerostomia and female gender or tobacco. In this series, a younger age was also associated to xerostomia.

In the group of elderly patients, multivariate analysis confirmed a significant association between xerostomia and the number of drugs taken per day. The multivariate model included, in addition to the forced variables, the variable 'use of sodium potassium pump inhibitor' treatment. This variable was no longer associated to xerostomia after adjustment (p = 0.28) and did not modify the association between 'use of antiseptic mouthwashes' and xerostomia, therefore it was removed from the final model (Table III). In elderly patients we only observed a tendency of association between xerostomia and psychotropic drugs consumption (Table III).

Table I. Description on the population included in the study.

	Middle-aged group (n = 60)	Elderly group (n = 60)
Mean age, years	44.0 (8.7)	84.5 (8.0)
Women	21 (35.0)	43 (71.7)
Tobacco use	45 (75.0)	1 (1.7)
Previous or current illicit drug addiction	26 (43.3)	1 (1.7)
HIV infection	41 (68.3)	1 (1.7)
HCV infection	41 (68.3)	1 (1.7)
Depressive disorders	29 (48.3)	13 (21.7)
Diabetes mellitus	2 (3.3)	10 (16.7)
Alzheimer's disease	0	2 (3.3)
Parkinson's disease	0	1 (1.7)
Sjögren's syndrome	0	1 (1.7)
Dehydration	0	0
Head and neck radiation therapy	0	0
Mean number of drugs taken per day	5.2 (1.2)	8.1 (3.2)
Loss of appetite	22 (36.7)	28 (46.7)
Recent non-voluntary weight loss	28 (46.7)	37 (61.7)
Mean Body Mass Index (BMI), kg/m2	22.8 (4.1)	23.6 (4.5)
Subjective xerostomia	37 (61.7)	38 (63.3)
Use of antiseptic mouthwashes >2 weeks	20 (33.3)	17 (18.3)
Oral candidiasis	8 (13.3)	1 (1.7)
Oral pain	13 (21.7)	12 (20.0)
Oral ulcerations	4 (6.7)	4 (6.7)
Active dental cariesa	25 (49.0)	1 (2.7)
Edentulousness (no residual tooth)	9 (15.0)	23 (38.3)
Removable denture(s)	27 (45.0)	25 (41.7)
Mean masticatory ability,b %	50.9 (31.5)	22.8 (30.6)

Results are expressed as mean (standard deviation) or number (%).
[a]The percentage of active dental caries was calculated in dentate patients only (51 younger and 37 elderly patients).
[b]Masticatory ability, expressed as a percentage, was recorded without removable dentures: an index to quantify the couples of antagonistic teeth (100%: 32 healthy teeth; 0%: no couple of antagonistic teeth).

Discussion

This study showed that, in a population of hospitalized adults taking polypharmacy (mean age = 44), the regular use of antiseptic mouthwashes was independently associated to xerostomia. Despite a high prevalence of xerostomia in patients who are administered polypharmacy (62.5% in the present series of 120 subjects), antiseptic mouthwashes had never been included in the list of the drugs associated with xerostomia. Apart from antiseptic mouthwashes, in the group of middle-aged patients we could not attribute xerostomia to any specific medication or pharmacodynamic pathway. Only 14 patients were given true anti-cholinergic drug (muscarinic antagonists), which was insufficient to correlate these drugs to xerostomia. These results are in line with those of previous authors with larger series, who did not evidence any association between xerostomia and xerogenic medications, other than true anti-muscarinic medications [3,16].

Many risk factors may be involved in xerostomia and the present study faced several difficulties. First, it is difficult to validly and reliably assess the degree of xerostomia [20,22]. Second, drugs classification is complex and we proposed a coding system based on pharmacodynamic rather than therapeutic classes. Finally, the present study was a cross-sectional study and causality between the use of mouthwashes and secondary mouth dryness or conversely the feeling of mouth dryness and secondary use of mouthwashes can be debated. However, a microbiological approach would favor the first hypothesis. Actually, antiseptic mouthwashes efficiently fight bacterial proliferation. The impact of antiseptic mouthwashes on mouth dryness could be explained by an unbalance of the endogenous microbial biofilm coating the oral mucosa. Eliasson et al. [23] showed that a feeling of xerostomia was related to a deficiency in minor salivary gland secretions. Mucin-rich saliva moistens the oral mucosal surfaces more efficiently than the salivary flows produced during meals by the parotid, submandibular and sublingual glands. Salivary mucins are glycoproteins with large oligosaccharides side chains able to sequester water and lubricate the oral mucosa [11]. They contribute to the extracellular matrix of the oral biofilm [24]. However, the healthy biofilm is also composed of bacteria, such as *Streptococcus salivarium*, *Streptococcus mitis*, *Rothia mucilaginosa*, *Gemella haemolysans* and *Fusobacterium nucleatum*, themselves enveloped by glycoproteic capsules or glycocalyx able to retain water [25,26]. These bacterial species are fully susceptible *in vitro* to antiseptics commonly used in oral care products, including quaternary ammonium, betain, resorcin, triclosan, essential oils and alcohol [6]. Fluorides also display antimicrobial properties against cariogenic and other viridans streptococci [27,28]. The unbalanced bacterial biofilm can in turn be colonized by *Candida albicans* [29], which is able to produce secretory aspartyl proteinases (Sap2), specifically known to disrupt mucins [30]. Use of antiseptic mouthwashes for a duration of time of more than 2 weeks could, thus, initiate or worsen mouth dryness by a direct action on the oral biofilm. Considering these preliminary results, microbial biofilm analysis would help to understand whether use of

Table II. Drug treatment of the population included in the study.

Drug treatment	Middle-aged group (n = 60)	Elderly group (n = 60)
Muscarinic antagonists	7 (11.7)	7 (11.7)
Adrenergic alpha-antagonists	11 (18.3)	14 (23.3)
Opioid agonists	21 (35.0)	15 (25.0)
Serotonin 2 (5-hydroxy-tryptamine 2, 5-HT2) blockers	5 (8.3)	9 (15)
Histamine 1 (H1) inhibitors	11 (18.3)	10 (16.7)
Dopamin 2 (D2) receptors blockers	7 (11.7)	7 (11.7)
Gamma-amino-butyric acid -A (GABA-A) receptor agonists	20 (33.3)	29 (48.3)
Paracetamol	2 (3.3)	37 (61.7)
Glucocoticoids	3 (5.0)	4 (6.7)
Antibacterial agents	8 (13.3)	4 (6.7)
Antifungal agents	4 (6.7)	3 (5.0)
Anti-HIV agents (non-nucleosidic reverse transcriptase inhibitors, NNRTI)	13 (21.7)	0
Anti-HIV agents (nucleotidic reverse transcriptase inhibitors, NRTI)	37 (61.7)	0
Anti-HIV agents (protease inhibitors, PI)	21 (35.0)	0
Diuretics	2 (3.3)	21 (35.0)
Adrenergic 1 beta-blockers	5 (8.3)	15 (25.0)
Angiotensin converting enzyme (ACE) inhibitors	0	25 (41.7)
Sodium potassium pump inhibitors (SPPI)	0	17 (28.3)
Iron supplements	1 (1.7)	9 (15.0)
Calcium channel blockers	0	13 (21.7)
Platelet aggregation inhibitors	2 (3.3)	13 (21.7)
Coumarin anticoagulants	2 (3.3)	8 (13.3)
Heparin	0	9 (15.0)
Proton pump inhibitors (PPI)	1 (1.7)	18 (30.0)
Antidiabetic agents	2 (3.3)	10 (16.7)
Psychotropic drugs[a]	17 (28.3)	27 (45.0)

Results are expressed as number (%).
[a]Psychotropic drugs: patients receiving muscarinic antagonists, adrenergic alpha-antagonists, opioid agonists, 5-HT2 blockers, H1 inhibitors, D2 receptor blockers and/or GABA-A receptor agonists.

mouthwashes exacerbates xerostomia among persons taking polypharmacy.

This study showed that hospital stay did not prevent tobacco smoking and confirmed that it was a risk factor of xerostomia [31]. In parallel with the present results, smoking could have systemic and topical effects on xerostomia. It is possible that the hospitalization contributes to reduce the tobacco consumption but we have no quantified data allowing us to compare before and after. The results are given according to the answers of patients and maybe under-estimated in particular for the sick of the Department of Geriatrics.

Among elderly people (mean age = 85), we did not find a significant link between complaints of mouth dryness and the regular use of antiseptic mouthwashes. The first explanation was that elderly patients were more heavily medicated than younger patients (average = 8.2 drugs/day vs 5.2 drugs/day) and the risk of xerostomia increases with the number of drugs taken daily [2]. However, other causes of mouth dryness among elderly could have been taken in account, such as age-related saliva alterations and mouth breathing [1,2]. Besides, elderly people in their 80s frequently suffer from swallowing problems. In order to avoid choking, they are given crushed medicines or opened capsules mixed with food [32]. A topical antimicrobial action of active ingredients on the oral biofilm cannot be excluded to explain the high prevalence of xerostomia among elderly patients taking polypharmacy. This would be in line with literature data, confirmed by the present study, assessing that the risk of dry mouth increases when patients are prescribed four or more drugs per day, whatever drugs are prescribed, except for true atropinic drugs which have a clear pharmacodynamic action on salivary secretory cells [3,16]. In other words, topical factors directly in contact with the oral mucosa, such as tobacco smoking, alcohol (in drinks or in mouthwashes), antiseptic mouthwashes or crushed medicines, could be inducers of xerostomia by disrupting the endogenous microbial biofilm [31–33].

According to recommended regimens, the duration of use of antiseptic mouthwashes should not exceed 2 weeks. However, in this study, many patients used them as if they were common hygiene products. They reported the 'expectation of improving dry mouth symptoms' or 'slowing down the progression of caries or periodontal diseases'. Antiseptic mouthwashes are also commonly recommended as daily oral care products to fight mouth dryness, dental caries and gingival inflammation in hospitals or at home [6,12,27,28]. As far as xerostomia may severely alter the quality-of-life of chronically ill or elderly patients [34–36], the use of antiseptic mouthwashes should be taken into account in patients taking polypharmacy.

In conclusion, patients and caregivers should be aware that long-term, routine use of the most common mouthwashes might be harmful and increase the risk of xerostomia, especially in patients taking polypharmacy. These antimicrobial products should be left aside and replaced by conventional oral hygiene procedures whenever xerostomia worsens quality-of-life or nutritional status, particularly with frail chronically ill patients.

Table III. Multivariate analysis for association with xerostomia in the middle-aged and in the elderly populations.

	Middle-aged patients (n = 60)		Elderly patients (n = 60)	
	OR (95% CI)	p	OR (95% CI)	p
Women	6.57 (1.1; 38.3)	0.036	1.06 (0.27; 4.2)	0.93
Age	1.14 (1.02; 1.28)	0.024	–	–
Use of antiseptic mouthwash >2 weeks	0.2 (0.04; 1.0)	0.052	0.59 (0.15; 2.3)	0.44
Tobacco use	0.09 (0.01; 0.63)	0.016	–	–
Number of drugs taken per day	0.83 (0.67; 1.0)	0.105	0.75 (0.57; 0.99)	0.042
Psychotropic drugs[a]	0.76 (0.15; 3.8)	0.74	0.30 (0.08; 1.11)	0.072

OR, Odds Ratio.
[a]Psychotropic drugs: patients receiving muscarinic antagonists, adrenergic alpha-antagonists, opioid agonists, 5-HT2 blockers, H1 inhibitors, D2 receptor blockers and/or GABA-A receptor agonists.

Additional studies would be necessary on the biofilm in the case of xerostomia. Research and quantification of bacterial species of the healthy oral biofilm capable of maintaining hydration due to their glycocalyx such as *Rothia mucilaginosa*, *Prevotella intermedia* or *Micrococcus luteus* would be particularly interesting. Usually these bacterial markers are not isolated and quantified in the studies on the oral mucosal flora.

Acknowledgments

This research was carried out without funding. We thank Dale Rosenbach, DMD, MS, for manuscript revision (Clinical Instructor & Course Director, Periodontics & Implant Dentistry at Woodhull Medical Center and Lutheran Medical Center, New York, USA).

***Declaration of interest*:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Visvanathan V, Nix P. Managing the patient presenting with xerostomia: a review. Int J Clin Pract 2010;64:404–7.
[2] Sreebny LM, Vissink A. editors. Dry mouth, the malevolent symptom: a clinical guide. 1srt ed. Singapore: Wiley-Blackwell; 2010.
[3] Glore RJ, Spiteri-Staines K, Paleri V. A patient with dry mouth. Clin Otolaryngol 2009;34:358–63.
[4] Nederfors T, Isaksson R, Mornstad H, Dahlof C. Prevalence of perceived symptoms of dry mouth in an adult Swedish population–relation to age, sex and pharmacotherapy. Community Dent Oral Epidemiol 1997;25:211–16.
[5] Chavez EM, Taylor GW, Borrell LN, Ship JA. Salivary function and glycemic control in older persons with diabetes. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000;89:305–11.
[6] Furness S, Worthington HV, Bryan G, Birchenough S, McMillan R. Interventions for the management of dry mouth: topical therapies. Cochrane Database Syst Rev 2011;12, doi: 10.1002/14651858.
[7] Deschasse G, Steenpass V, Couturier P, Diot I, Maruani A, Maillot F. Sicca syndrome in hospitalized older adults: prevalence and comparison of objective and subjective symptoms. J Am Geriatr Soc 2011;59:2178–9.
[8] Glazar I, Urek MM, Brumini G, Pezelj-Ribaric S. Oral sensorial complaints, salivary flow rate and mucosal lesions in the institutionalized elderly. J Oral Rehab 2010;37:93–9.
[9] Persson K, Olin E, Ostman M. Oral health problems and support as experienced by people with severe mental illness living in community-based subsidised housing - A qualitative study. Health Soc Care Community 2010;18:529–36.
[10] Samnieng P, Ueno M, Shinada K, Zaitsu T, Wright FA, Kawaguchi Y. Association of hyposalivation with oral function, nutrition and oral health in community-dwelling elderly Thai. Community Dent Health 2012;29:117–23.
[11] Hitz Lindenmüller I, Lambrecht JT. Oral care. Curr Probl Dermatol 2011;40:107–15.
[12] Vissink A, Mitchell JB, Baum BJ, Limsand KH, Jensen SB, Fox PC, et al. Clinical management of salivary gland hypofunction and xerostomia in head-and-neck cancer patients: successes and barriers. Int J Radiat Oncol Biol Phys 2010;78:983–91.
[13] Femiano F, Rullo R, di Spirito F, Lanza A, Festa VM, Cirillo N. A comparison of salivary substitutes versus a natural sialogogue (citric acid) in patients complaining of dry mouth as an adverse drug reaction: a clinical, randomized controlled study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;112:e15–20.
[14] Castro I, Sepulveda D, Cortès J, Quest AF, Barrera MJ, Bahamondes V, et al. Oral dryness in Sjögren's syndrome patients. Not just a question of water. Autoimmun Rev 2013;12:567–74.
[15] Borges BC, Fulco GM, Souza AJ, de Lima KC. Xerostomia and hyposalivation: a preliminary report of their prevalence and associated factors in Brazilian elderly diabetic patients. Oral Health Prev Dent 2010;8:153–8.
[16] Desoutter A, Soudain-Pineau M, Munsch F, Mauprivez C, Dufour T, Coeuriot JL. Xerostomia and medication: a cross-sectional study in long-term geriatric wards. J Nutr Health Aging 2012;16:575–9.
[17] Thomson WM, Poulton R, Broadbent JM, Al-Kubaisy S. Xerostomia and medications among 32-year-olds. Acta Odontol Scand 2006;64:249–54.
[18] Teles RP, Teles FR. Antimicrobial agents used in the control of periodontal biofilms: effective adjuncts to mechanical plaque control? Braz Oral Res 2009;23:39–48.

[19] Humphrey SP, Williamson RT. A review of saliva: normal composition, flow, and function. J Prosthet Dent 2001;85: 162–9.
[20] Thomson WM, Lawrence HP, Broadbent JM, Poulton R. The impact of xerostomia on oral-health related quality of life among younger adults. Health Qual Life Outcomes 2006; 4:86, doi: 10.1186/1477-7525-4-86.
[21] Madinier I, Starita-Geribaldi M, Berthier F, Pesci-Bardon C, Brocker P. Detection of mild hyposalivation in the elderly based on the chewing time of specifically-designed disc-tests: diagnostic accuracy. J Am Geriatr Soc 2009;57:691–6.
[22] Thomson WM, van der Putten GJ, de Baat C, Ikebe K, Matsuda K, Enoki K, et al. Shortening the xerostomia inventory. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;112:322–7.
[23] Eliasson L, Birkhed D, Carlen A. Feeling of dry mouth in relation to whole and minor gland saliva secretion rate. Arch Oral Biol 2009;54:263–7.
[24] Dongari-Bagtozoglou A. Pathogenesis of mucosal biofilm infections: challenges and progress. Expert Rev Anti Infect Ther 2008;6:201–8.
[25] Kazor CE, Mitchell PM, Lee AM, Stokes LN, Loesche WJ, Dewhirst FE, et al. Diversity of bacterial population on the tongue dorsa of patients with halitosis and healthy patients. J Clin Microbiol 2003;41:558–63.
[26] Candela T, Moyna M, Haustant M, Fouet A. Fusobacterium nucleatum, the first Gram-negative bacterium demonstrated to produce polyglutamate. Can J Microbiol 2009;55: 627–32.
[27] Barnett ML. The rationale for the daily use of an antimicrobial mouthrinse. J Am Dent Assoc 2006;137(Suppl):16–21.
[28] Su N, Marek CL, Ching V, Grushka M. Caries prevention for patients with dry mouth. J Can Dent Assoc 2011;77:b85.
[29] Torres SR, Peixoto CB, Caldas DM, Akitit T, Barreiros MG, de Uzeda M, et al. A prospective randomized trial to reduce oral Candida spp. colonization in patients with hyposalivation. Braz Oral Res 2007;21:182–7.
[30] Colina AR, Aumont F, Deslauriers N, Belhumeur P, de Repentigny L. Evidence for degradation of gastrointestinal mucin by Candida albicans secretory aspartyl proteinase. Infect Immun 1996;64:4514–19.
[31] Rad M, Kakoie S, Niliye Brojeni F, Pourdaghan N. Effect of long-term smoking on whole-mouth salivary flow rate and oral health. Dent Res Dent Clin Dent Prospects 2010;4:110–14.
[32] Stubbs J, Haw C, Dickens G. Dose form modification - a common but potentially hazardous practice. A literature review and study of medication administration to older psychiatric inpatients. Int Psychogeriatr 2008;20:616–27.
[33] Friedlander AH, Marder SR, Pisegna JR, Yagiela JA. Alcohol abuse and dependence: psychopathology, medical management and dental implications. J Am Dent Assoc 2003;134:731–40.
[34] Ikebe K, Morii K, Kashiwagi J, Nokubi T, Ettinger RL. Impact of dry mouth on oral symptoms and function in removable denture wearers in Japan. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;99:704–10.
[35] Locker D. Dental status, xerostomia and the oral health-related quality of life of an elderly institutionalized population. Spec Care Dent 2003;23:86–93.
[36] Agha-Hosseini F, Mirzaii-Dizgah I, Mirjalili N. Relationship of stimulated whole saliva cortisol level with the severity of a feeling of dry mouth in menopausal women. Gerodontology 2012;29:43–7.

CHAPITRE II

TASTE OF TEN DRUGS FREQUENTLY PRESCRIBED IN NURSING HOMES CRUSHED AND MIXED IN FOOD: OBSERVATIONAL STUDY IN 16 HEALTHY VOLUNTEERS

J. Lamure [a,b,*], P. Brocker [c], S.M. Schneider [d], R. Collomp [e], F. Bertin-Hugault [f], P. Denormandie [g], I. Prêcheur [a,b]

Published in

Jour Nursing Home Res 2015; 1:55-61

CHAPITRE I – Avant-propos

Résumé

Les personnes âgées (PA) dépendantes souffrent souvent de pathologies chroniques et sont polymédiquées. Dans des établissements d'hébergement pour personnes âgées dépendantes (EHPAD), les résidents prennent en moyenne 6 à 8 principes actifs / jour (Source pôle Gérontologie, CHU de Nice) ce qui correspond à 10 à 20 prises de médicaments par jour. Mais 40 % des résidants ont des troubles de la déglutition ou des troubles du comportement : les soignants sont obligés d'écraser les comprimés et les gélules et de les donner mélangés dans une compote, un laitage, de l'eau gélifiée… Des organismes, comme certaines OMEDIT ont publié une liste des médicaments autorisés à être écrasés, car cette pratique peut modifier la pharmacocinétique de certains médicaments, et les rendre inactifs voire toxiques. L'hypothèse est que les médicaments écrasés pourraient aussi modifier le goût des aliments. Cela pourrait entraîner un refus de manger et, outre l'impact clinique lié à la non prise de médicaments, contribuer à l'anorexie et à la dénutrition des malades âgés. L''aspect gustatif de cette pratique a peu été évalué. Pourtant, la dénutrition augmente les risques d'infections, de chutes, de fractures, d'escarres, de dépression et la dépendance. Cette étude a pour but d'améliorer la qualité de vie des personnes âgées dépendantes au moment des repas, d'aider familles et soignants à lutter contre l'anorexie et la dénutrition tout en renforçant la qualité et la sécurité de la prise en charge médicamenteuse des PA.

Type d'étude : il s'agit d'une étude observationnelle de cohorte, avec un test hédonique, descriptif, en une séance, pour tester le goût de 10 médicaments écrasés dans de l'eau gélifiée et de la compote de pomme.

Objectif principal : identifier chez des volontaires sains, sur le volet gustatif, quels médicaments il est acceptable ou déconseillé d'ajouter une fois écrasés ou ouverts dans les aliments.

Matériels et Méthodes :

Volontaires participant à l'étude. Les évaluateurs seront 16 volontaires sains : 8 professionnels de la restauration, des arômes alimentaires, de la nutrition et de la diététique, et 8 médecins, pharmaciens, chirurgiens-dentistes, infirmiers et/ou aides-soignants du CHU de Nice.

Critères d'inclusion : adultes volontaires en bonne santé, sans allergie connue aux 10 médicaments à tester.

Critères d'évaluation :

1) quantitatif : note de 0 (pas bon) à 10 (bon : pas de goût ou de gêne particuliers) pour l'eau gélifiée et la compote et

2) qualitatif : description de l'arôme perçu (acide, amer, sucré, salé, astringent, piquant, aromatique…).

16 volontaires sains ont testé les 10 médicaments les plus prescrits dans les EHPAD du groupe Korian et identifiés comme pouvant être écrasés ou ouverts, en présence d'un médecin urgentiste et d'un toxicologue (goûteurs). Les médicaments ont été écrasés dans de l'eau gélifiée et de la compote : 10 médicaments séparés, 1 mélange de 6 et 1 comparateur (eau gélifiée et compote non modifiées). Chaque volontaire réalisa ces 24 tests en aveugle et a rempli une feuille de résultats. Il recrachera et se rincera la bouche avec de l'eau entre deux tests ; la dose susceptible d'être ingérée sera d'environ 1/500ème d'une dose unitaire. Excepté un risque d'allergie, le risque médical est donc négligeable pour les goûteurs. La levée de l'aveugle aura lieu immédiatement après la fin du test.

Résultats :

En faisant la moyenne des deux supports (eau gélifiée et compote), les notes les plus basses ont été attribuées au mélange de paracétamol, alprazolam, furosémide, lévothyroxine

sodique, mémantine et zopiclone (1,5 ± 1,6 ; 0 à 5), suivi du zopiclone (1,9 ± 2,3 ; 0 à 8) ; du clopidogrel (4,3 ± 2,1 ; 1 à 7) et du paracétamol (4,6 ± 1,8 ; 1 à 8). Tous ces médicaments ont provoqué une sensation d'amertume très désagréable et persistante. Le zopiclone, notamment, seul et mélangé à l'eau gélifiée, a été qualifié "d'immangeable, insupportable, inacceptable, très mauvais, très désagréable, terrible, pas supportable, impossible à manger, pas possible".

L'eau gélifiée et la compote sans médicament, utilisées comme contrôle, ont été goûtées de façon aléatoire au milieu des autres verrines, et notées respectivement 6,7 ± 1,4 (4 à 9) et 7,1 ± 1,1 (5 à 9,5). Cela montre qu'un aliment « normal » peut sembler mauvais après la prise de médicaments écrasés. Enfin, les autres notes ont varié de 6,1 à 7,9 pour l'alprazolam, le ramipril, l'oxazépam, la lévothyroxine sodique, le donépézil et le furosémide.

Conclusion :

Le goût amer de certains médicament peut être insupportable, quand ils sont écrasés et mélangés dans de la nourriture. La pire expérience a été le mélange de 6 médicaments. Mais il existe des différences d'appréciations importantes d'une personne à l'autre et d'un principe actif à l'autre. Idéalement, il faudrait organiser des ateliers du goût, pour que chaque patient puisse tester séparément chaque médicament de sa prescription. Les soignants devraient éviter de mélanger un médicament qui a un mauvais goût avec d'autres médicaments, parce que cela provoque la non-observance de l'ensemble de la prescription et un refus de l'aliment, voire du repas. Si le mauvais goût d'un médicament écrasé provoque le refus du médicament, les infirmiers et les aides-soignants devraient en informer le médecin prescripteur et le pharmacien qui délivre les médicaments, afin qu'ils trouvent des solutions alternatives (arrêt du médicament ou substitution par un autre principe actif ou une autre forme galénique ; « pause » sans médicament au repas de midi). Les soignants

pourraient aussi proposer au patient d'autres aliments, par exemple plus sucrés (une cuillère de confiture) ou d'autres conditions d'administration (sous un plus petit volume, à la fin du repas...). A moyen terme, les laboratoires pharmaceutiques pourraient développer des formulations galéniques adaptées aux personnes âgées, comme ils le font déjà pour les enfants

TASTE OF TEN DRUGS FREQUENTLY PRESCRIBED IN NURSING HOMES CRUSHED AND MIXED IN FOOD: OBSERVATIONAL STUDY IN 16 HEALTHY VOLUNTEERS

J. LAMURE[1,2], P. BROCKER[3], S.M. SCHNEIDER[4], R. COLLOMP[5], F. BERTIN-HUGAULT[6], P. DENORMANDIE[7], I. PRÊCHEUR[1,2,3]

1. Department of Dentistry, Nice University Hospital, Nice, France; 2. Micoralis Laboratory, Faculty of Dentistry, University of Nice Sophia Antipolis, Nice, France; 3. Department of Geriatrics, Nice University Hospital, Nice, France; 4. Department of Nutrition, Nice University Hospital, Nice, France; 5. Pharmacy, Nice University Hospital, Nice, France; 6. Department of Geriatrics, Assistance Publique Hôpitaux de Lyon, Lyon, France; 7. Institut du bien vieillir Korian, Groupe Korian, Paris, France. Corresponding author: J. Lamure, Micoralis Laboratory, Faculty of Dentistry, 24 avenue des Diables Bleus, 06357 Nice cedex 4, France. Tel.: +33 4 92 00 11 00. E-mail address: drjulielamure@gmail.com

Abstract: *Background & Aims:* Many frail elderly patients are polymedicated. Whether they suffer from dysphagia (due to stroke, Parkinson's disease, etc.) or cognitive troubles (due to Alzheimer's disease, etc.), they are often given blended food, with drugs crushed and mixed into the food. Health Authorities recommend to crush and to administrate crushed drugs separately, for pharmacologic reasons, but the drugs are usually mixed together to facilitate ease of case by nursing staff. Crushed drugs can have a bad taste, leading to drug / food refusal, worsening malnutrition, but this qualitative aspect has been scarcely studied in geriatric populations. The present study aimed to evaluate the taste of the ten drugs most frequently prescribed in nursing homes, in order to determine which drugs are acceptable or not when crushed and mixed into food. *Methods:* This one-step observational study was designed like a food or wine tasting. A jury of healthy volunteers was recruited among medical staff (8 volunteers) and other people involved in food and gastronomy (8 volunteers, including a starred Chef). Every tablet or capsule was mixed into 100 mL of berry-flavored jelly or apple sauce. It was a blind tasting of 24 verrines, containing the ten drugs randomly distributed, a control without drug and a combination of the 6 top-list drugs. Twelve jelly verrines were followed by 12 apple sauce verrines. Tasters spat the spoonful content out after they had assessed its taste. Each verrine was scored from 0 (bad taste) to 10 (good). Qualitative and free comments were also recorded. *Results:* The lowest scores were attributed to the combination of paracetamol, alprazolam, furosemide, levothyroxine sodium, memantine and zopiclone (1.5 ± 1.6; 0 to 5), followed by zopiclone (1.9 ± 2.3; 0 to 8), clopidogrel (4.3 ± 2.1; 1 to 7) and paracetamol (4.6 ± 1.8; 1 to 8). All these drugs had a long-lasting bitterness. Zopiclone mixed and alone was qualified as unbearable and one participant exhibited nausea by taking it. Five participants did not take lunch after the study for lack of hunger (5/16: 31.3 %). Drug-free jelly and apple sauce were scored 6.7 ± 1.4 (4 to 9) and 7.1 ± 1.1 (5-9.5), respectively. Other scores ranged from 6.1 to 7.9, for alprazolam, ramipril, oxazepam, levothyroxine sodium, donezepil and furosemide. *Conclusions:* The taste of some drugs may be unbearable when they are crushed and mixed into food, and caregivers should avoid mixing a bad-tasting drug with the other drugs. There are wide differences of taste acceptability from one person to another. Thus, during workshops, every patient could taste once separately any single drug in his prescription list. If a bad taste leads to drug refusal, caregivers should inform physicians and pharmacists, who in turn should seek alternative medical solutions (drug discontinuation or substitution). Caregivers could also seek alternative food or administration conditions. On a mid-term basis, pharmaceutical companies should also develop specific pharmaceutical forms, as they do for children.

Key words: Food-drug interactions, frail elderly, malnutrition, swallowing disorders, taste.

Introduction

Elderly people frequently suffer from chronic diseases and are consequently often polymedicated. In nursing homes and geriatric hospital wards, they are administered a daily average of 6 to 8 drugs, corresponding to 6 to 20 tablets, pills or capsules (1). The prevalence of dysphagia increases with age: at least 15% of the elderly population and over 50% of residents in nursing homes are affected by dysphagia due to stroke, cancer, Parkinson's disease, Alzheimer's disease, Sjögren's syndrome and some medications that can cause xerostomia. Dysphagia increases the risk of aspiration pneumonia. The consequent beverage and food refusal can lead to dehydration, anorexia, malnutrition and potentially even death. As a precaution, these patients are often given blended food (2). Nursing staff is also obliged to crush tablets, to open capsules, and to mix drugs into textured food, frequently made with blenders.

Crushing drugs can induce chemical (e.g. oxidization, acid-basic interaction) and pharmacologic problems (such as with gastro-resistant tablets) (3). Listing of drugs authorized for crushing and consensual recommendations for their administration have been published by several groups of experts (4, 5). According to recommendations: (1) physicians should limit drug prescription, (2) pharmacists should propose alternative formulation such as oral drops whenever possible, and (3) nurses should only crush authorized drugs, they should

Received April 23, 2015
Accepted for publication May 26, 2015

do so separately just before administration and they should mix them into separated food servings (3). Usually, nurse's aides are charged with giving both food and drugs to patients, and so this task often falls on them. Soft/liquid and sweet food under a small volume is generally preferred, such as jelly, apple sauce or dairy products (100 to 125 mL/serving).

In nature, many poisons are alkaloids stimulating bitter taste receptors, and bitterness mediates an aversive response to toxic food (6). Many drugs have a bitter taste, too, and when they are crushed into food, there is a risk of developing food aversion. But the sensorial aspect of crushing drugs has scarcely been studied in geriatric populations. Published studies focus mainly on anti-inflammatory medicines (prednisolone, diclofenac), antimalarial medicines (mefloquine, artemether, lumefantrine) and antihypertensives (amlodipine, candesartan, etc.), generally involving pediatric patients (5–12)

The present study aimed to evaluate the taste of the ten drugs most frequently prescribed in nursing homes, in order to determine which drugs are acceptable or not when crushed into food, from a sensorial point of view. The medical objective is to limit drug refusal and anorexia. The study was designed like any food or wine tasting, with a jury of healthy volunteers recruited among medical staff (eight volunteers) and other people involved in food and gastronomy field (eight volunteers).

Material and methods

The study was a one-step observational study carried out in June 2014 in the Department of Clinical Research of the Nice University Hospital. It was a phase I study with a cohort of 16 volunteers (Table 1). Investigators and participants were unpaid. Participants were recruited by the investigators in professional and personal settings. Non-inclusion criteria were untreated severe disease, allergy to any of the drugs to be tested, age over 70, pregnancy or breast-feeding. Current drug prescription was not an exclusion criterion. The morning of the study, just before the test session, the main investigator in charge of the study performed medical consultations and obtained written informed consent from all of the participants. They were given an emergency hospital phone number available night and day for a one-week follow-up, if necessary.

The ten drugs tested were selected as the top-list of the drugs prescribed in 2013 in the 596 nursing homes of the Groupe Korian, in France, Germany, Italy and Belgium. Only tablets or capsules with crushing authorization were selected (4, 5) . Whenever applicable, the lowest dosage was selected. The drugs were provided by the hospital pharmacy. Every tablet or capsule was mixed into 100 mL of berry-flavored jelly (Valade, France) or apple sauce (Andros, France). A volume of 5 mL of each preparation was distributed in small transparent plastic cocktail cups (verrines) and served with 1 mL-containing

Table 1

Taste of ten crushed drugs: scores attributed by the 16 volunteers

Participant : profession (gender)	Drug taste : mean score into jelly [a]	Drug taste : mean score into apple sauce [b]	Drug taste : general score [c]
Psychologist (W [d])	3.9 ± 2.2 (0-6)	5.2 ± 3.1 (0-8)	4.5 ± 2.7 (0-8)
Dermatologist (M [e])	4.2 ± 2.9 (0-8)	4.8 ± 3.6 (0-9)	4.5 ± 3.2 (0-9)
Geriatrician (M)	4.5 ± 2.4 (0-8)	5.1 ± 2.6 (0-7)	4.8 ± 2.5 (0-8)
Dental surgeon (M)	4.6 ± 2.3 (0-8)	5.5 ± 1.6 (2-7)	5.0 ± 2.0 (0-8)
Nurse's aide (M)	4.7 ± 1.7 (0-6)	5.3 ± 2.5 (0-8)	5.0 ± 2.1 (0-8)
Retired pensioner (M)	4.3 ± 1.6 (2-8)	6.1 ± 1.7 (2-7)	5.2 ± 1.9 (2-8)
Medical nutrition company worker (M)	5.6 ± 2.1 (2-8)	5.2 ± 2.3 (3-8)	5.4 ± 2.2 (2-8)
Medical nutrition company worker (W)	5.7 ± 2.1 (1-7)	5.6 ± 2.4 (1-8)	5.6 ± 2.2 (1-8)
Starred Chef (M)	6.0 ± 1.9 (1-7)	5.8 ± 2.6 (1-8)	5.9 ± 2.2 (1-8)
Geriatrician (W)	5.3 ± 3.0 (0-9)	6.4 ± 3.4 (0-9)	5.9 ± 3.2 (0-9)
Wedding planner (W)	6.3 ± 2.3 (2-8)	5.6 ± 2.5 (2-9)	6.0 ± 2.4 (2-9)
Nutritionist (M)	5.1 v 2.0 (0-7)	6.9 ± 3.1 (0-10)	6.0 ± 2.7 (0-10)
Pharmacist (M)	6.3 ± 2.1 (1-8)		
Dental surgeon (W)	6.3 ± 3.5 (1-10)	6.2 ± 3.4 (1-10)	6.3 ± 3.4 (1-10)
Nursing home administrative assistant (W)	7.4 ± 1.2 (5-8)	7.5 ± 1.0 (5-8)	7.4 ± 1.1 (5-8)
Retired pensioner (W)	7.3 ± 1.1 (5-8)	7.6 ± 1.0 (5-8)	7.5 ± 1.0 (5-8)

a,b,c Scoring ranged from 0 (bad taste) to 10 (good taste): mean score, standard deviation and extreme values attributed to the 12 verrines containing jelly a, to the 12 verrines containing apple sauce b and to the 24 verrines (jelly and apple sauce) c ; d W: women; e M: men

Table 2
Taste of ten drugs crushed and mixed into jelly or apple sauce

Drug tested (brand name)	Formulation	Main indication	Drug taste: mean score in jelly [a]	Drug taste : mean score in apple sauce [b]	Drug taste : general score [c]
Combination of 6 drugs: paracetamol, alprazolam, furosemide, levothyroxine, memantine, zopiclone			1.5 ± 1.6 (0-5)	1.5 ± 1.6 (0-5)	1.5 ± 1.6 (0-5)
Zopiclone (Imovane®)	Film-coated tablet 3.75 mg	Hypnotic, related to benzodiazepines	2.5 ±2.1 (0-8)	1.9 ± 2.3 (0-8)	2.2 ± 2.2 (0-8)
Clopidogrel (Plavix®)	Film-coated tablet 75 mg	Anti-platelet	4.3 ± 2.1 (1-7)	4.6 ± 2.2 (1-9)	4.5 ± 2.1 (1-9)
Paracetamol (Doliprane®)	Capsule 500 mg	Analgesic	4.6 ± 1.8(1-8)	5.8 ± 2.1 (1-8)	5.2 ± 2.0 (1-8)
Alprazolam (Alprazolam Mylan® generic of Xanax®)	Tablet 0.25 mg	Anxiolytic benzodiazepine	6.4 ± 1.4 (4-9)	6.7 ± 1.3 (4-9)	6.5 ± 1.4 (4-9)
Ramipril (Triatec®)	Film-coated tablet 1.25 mg	Antihypertensive, angiotensin converting enzyme inhibitor	7.2 ± 1.4 (4-10)	6.7 ± 2.1 (1-10)	7.0 ± 1.7 (1-10)
Oxazepam (Seresta®)	Tablet 50 mg	Anxiolytic benzodiazepine	6.4 ± 1.8 (3-9)	6.9 ± 1.6 (3-10)	6.6 ± 1.7 (3-10)
Control	Plain jelly or apple sauce		6.7 ± 1.4 (4-9)	7.1 ± 1.1 (5-9.5)	-
Memantine (Ebixa®)	Film-coated tablet 20 mg	Proposed against Alzheimer's disease	6.1 ± 1.5 (4-9)	7.2 ± 1.1 (5-9)	6.6 ± 1.4 (4-9)
Levothyroxine sodium (Levothyrox®)	Tablet 25 μg	Thyroid hormone	6.8 ± 1.5 (4-9)	7.4 ± 1.3 (5-10)	7.0 ± 1.4 (4-10)
Donepezil (Aricept®)	Film-coated tablet 5 mg	Acetycholinesterase inhibitor proposed against Alzheimer's disease	6.2 ± 1.6 (3-8)	7.4 ± 1.0 (6-9)	7.4 ± 1.0 (3-8)
Furosemide (Lasilix®)	Tablet 20 mg	Antihypertensive, loop diuretic	7.0 ± 1.2 (5-10)	7.9 ± 1.1 (6-10)	7.5 ± 1.1 (6-10)

a,b,c Scoring ranged from 0 (bad taste) to 10 (good taste): mean score, standard deviation and extreme values attributed to the 12 verrines containing jelly a, to the 12 verrines containing apple sauce b and to the 24 verrines (jelly and apple sauce) c

disposable coffee spoons. We assumed that each volunteer would taste two spoons of each mixture, corresponding to 1/50 of every tablet or capsule. After mouth rinse with flat bottled water (Evian, France), the residual quantity of food available for swallowing was estimated to 0.1 mL. The residual quantity of drugs available for swallowing was thus evaluated to 1/500 of every drug/verrine tasted. There was a blind tasting of 24 verrines, containing ten drugs, a control without drug and a combination of the 6 top-list drugs, corresponding to 12 jelly verrines followed by 12 apple sauce verrines. After tasting, tasters spit out the spoonful contents into a disposable plastic cup. The protocol was approved by the local Ethics Committee and registered by Health Authorities under Eudract n° 2013-003461-34.

This pilot study involved mostly non-professional food tasters. The investigation was limited to 16 participants, as it was a descriptive study without group comparison and no minimal number was required for statistical analysis. The main outcome assessment was a score attributed to each verrine containing crushed drugs or negative controls, ranging from 0 (bad taste) to 10 (good taste). The results were expressed as a mean score and standard deviation calculated for the 16 volunteers. Secondary outcomes were a tentative attribution to common flavors (sugary, sweet, sour, bitter, salty, astringent, prickling, aromatic, etc.) and free comments (6). All participants were recalled for possible post-study comments.

The order of drug serving was randomized in two blocks (jelly and apple sauce). Each verrine was assigned a number ranging from 1 to 24, beginning with jelly (1-12) and ending with apple sauce (13-24). The drugs were crushed and mixed by a nurse of the Clinical Research Department in a separate room. Participants were blinded to verrines contents and were not allowed to voice their tasting evaluation aloud. Each mouthful was spat into a disposable opaque plastic cup. In addition to bottled water, participants were offered white bread and green apples to clean their mouth between verrines, as with wine and food tasting protocols.

Table 3
Qualitative evaluation of ten crushed drugs: number of positive qualifier on the taste

Drugs tasted	Crushed into	Sugary	Aromatic	Sweet	Good	Total
Combination of 6 drugs [a]	jelly	0	0	0	0	0
Combination of 6 drugs [a]	apple sauce	1	0	0	0	1
Zopiclone	jelly	1	0	0	0	1
Zopiclone	apple sauce	1	0	0	0	1
Clopidogrel	apple sauce	2	1	0	0	3
Clopidogrel	jelly	4	2	0	1	7
Paracetamol	jelly	4	1	2	1	8
Ramipril	apple sauce	7	2	0	0	9
Alprazolam	apple sauce	8	2	0	0	10
Paracetamol	apple sauce	7	3	0	0	10
Control	apple sauce	9	2	1	0	12
Levothyroxine sodium	apple sauce	9	2	1	0	12
Memantine	jelly	7	1	0	4	12
Control	jelly	5	1	1	6	13
Alprazolam	jelly	8	3	2	1	14
Oxazepam	apple sauce	9	4	1	0	14
Donezepil	jelly	6	3	1	5	15
Furosemide	apple sauce	10	2	1	2	15
Oxazepam	jelly	9	1	0	5	15
Donezepil	apple sauce	11	3	2	0	16
Memantine	apple sauce	10	2	2	2	16
Levothyroxine sodium	jelly	7	3	3	4	17
Furosemide	jelly	12	2	3	1	18
Ramipril	jelly	10	6	4	4	24
Total		157	46	24	36	263

a. Combination of six drugs: paracetamol, alprazolam, furosemide, levothyroxine sodium, memantine, zopiclone

Results

Sixteen participants eligible for the study were recruited from Nice (France) and Monaco (Principality of Monaco). The cohort was comprised of four physicians (two geriatricians, a nutritionist and a dermatologist), a pharmacist, two dental surgeons, a nurse's aide, a psychologist, a Michelin starred Chef, a wedding planner, a nursing home administrative assistant, two retired pensioners and two members of a company specializing in oral nutritional supplements. The pharmacist had to leave the protocol following the first half of the study (immediately following the jelly test portion) because of professional reasons. There were nine men and seven women, aged 27 to 69. As for a formal tasting, participants were asked to avoid morning coffee or tea as well as perfumed cosmetics before the test. In order to preserve their anonymity, they were not introduced to each other. The drug tasting lasted from 9 to 10:30 in the morning. The mean scores attributed by the 16 volunteers are detailed in Table 1.

The randomized order of tasting in jelly was as follows: ramipril, alprazolam, combination of six drugs, zopiclone, paracetamol, furosemide, levothyroxine sodium, memantine, oxazepam, clopidogrel, negative control (jelly) and donezepil. There was a 5 min pause between the tasting of jelly and apple sauce verrines. The randomized order of tasting in apple sauce was as follows: furosemide, clopidogrel, donezepil, memantine, negative control (apple sauce), paracetamol, oxazepam, levothyroxine sodium, alprazolam, combination of six drugs, zopiclone and ramipril. The lowest scores were attributed to the combination of six drugs, followed by zopiclone, clopidogrel and paracetamol. The scores attributed to the ten drugs are detailed in Table 2.

Qualitative evaluation is detailed in Table 3 and 4. Table 3

Table 4
Qualitative evaluation of ten crushed drugs: number of negative qualifier on the taste

Drugs tasted	Crushed into	Salty	Prickling	Astringent	Sour	Bitter	Persistent	Total
Clopidogrel	jelly	2	1	2	3	11	7	26
Combination of 6 drugs [a]	jelly	1	1	2	4	14	3	25
Combination of 6 drugs [a]	apple sauce	1	2	2	4	10	4	23
Zopiclone	jelly	1	1	0	2	14	3	21
Zopiclone	apple sauce	1	1	1	1	13	4	21
Clopidogrel	apple sauce	0	0	0	4	9	3	16
Alprazolam	jelly	0	2	3	2	6	0	13
Paracetamol	jelly	2	1	2	2	3	0	10
Paracetamol	apple sauce	0	1	1	2	6	0	10
Ramipril	apple sauce	0	0	1	2	4	1	8
Mémantine	jelly	1	2	0	0	4	0	7
Alprazolam	apple sauce	0	0	0	0	6	0	6
Mémantine	apple sauce	0	0	2	1	1	2	6
Control	apple sauce	0	2	1	1	0	0	4
Donezepil	apple sauce	0	0	1	2	1	0	4
Oxazepam	jelly	0	1	0	0	2	1	4
Oxazepam	apple sauce	0	0	0	1	2	1	4
Donezepil	jelly	0	0	0	2	1	0	3
Ramipril	jelly	1	1	0	0	1	0	3
Control	jelly	0	0	0	1	1	0	2
Furosemide	apple sauce	0	0	0	2	0	0	2
Levothyroxine sodium	jelly	0	0	0	1	1	0	2
Furosemide	jelly	0	0	0	0	0	0	0
Levothyroxine sodium	apple sauce	0	0	0	0	0	0	0
Total		10	16	18	37	110	29	220

a. Combination of six drugs: paracetamol, alprazolam, furosemide, levothyroxine sodium, memantine, zopiclone

and 4 record how many times each qualifier was mentioned on the record cards, either as a positive (pleasant) or a negative (unpleasant) comment. In addition to the score, some drugs were attributed qualitative comments. Quantitative (Table 2) and qualitative (Table 3 and 4) evaluations allowed similar ranking of the drugs, as regards the pleasure (or lack thereof) to taste them. The psychologist recorded that she almost experienced nausea by taking the verrines containing zopiclone alone in jelly as well as combined with other medications in jelly, but not into apple sauce. Nearly one third of participants (5/16 or 31.3%) did not wish to take lunch after the study because of anorexia. There were no other side effects reported during the week following the study. The words «unedible, unbearable, unacceptable, very bad, very unpleasant, terrible, not bearable, impossible to ingest, no way» were used to describe the bitterness and long-lasting bitter taste of zopiclone, alone and combined with other drugs. Clopidogrel and paracetamol also had negative comments, but not as severe.

Discussion

The key result of this study was the wide difference of taste among the ten crushed drugs tested. One crushed drug had an unbearably strong and long-lasting bitterness (zopiclone), and two others had a very pronounced bitterness (clopidogrel, paracetamol). A combination of six drugs containing both zopiclone and paracetamol elicited the worst response. Conversely, the seven other drugs tested were scored from acceptable to good (alprazolam, ramipril, oxazepam, memantine, levothyroxine sodium, donezepil and furosemide). Short or long-lasting bitterness were the main concerns, but unpleasant tastes such as salty, prickling, astringent and sour

were also reported. There was a huge variability between drugs, but also, though in a lesser way, between users. The qualitative evaluation, detailed in Table 3 and 4, is not really relevant in this study. However the qualitative description of the taste is part of regular tasting session protocols and had to be done in this study in order to be complete. We won't do further investigations on qualitative descriptions.

Being a pilot study, this work suffered from several biases and inaccuracies. Among these was the limited number of participants; the bitter drugs probably altered the taste perception of the subsequent verrines; a series of 24 consecutive tests was probably excessive; the crushed drugs were mixed only into jelly and apple sauce but not in dairy products; a 5-point scale or less could have been more reliable; etc. (7–10). In 2014, Uestuener et al. (10) designed a protocol to taste acceptability of amlodipine and candersartan. According to these authors, there was no taste difference between pulverized brand-name and generics. The participants were health care professionals, including 19 nurses and 12 physicians (10). The originality of the present study was to involve people working in the field of food and gastronomy in a pharmacological study. All in all, this study was unpleasant but safe for participants and, in addition to zopiclone, clopidogrel and to a lesser extent paracetamol, other drugs with a bad taste could be identified. Last, age and disease are known to induce taste modifications (1–3), and therefore reports from healthy volunteers may not match results in the target population.

Despite recommendations, it is commonly observed that several drugs are crushed together and administered in the same food (3). Actually, a single drug with a bad taste can induce patient's refusal, leading to non-compliance with the entire regimen, followed by meal refusal, anorexia and malnutrition. In turn, malnutrition increases the risk of infections, falls, bed sores and depression, the length of hospital stay and loss of autonomy and thus increases drugs consumption (11). Several approaches could be possible to combat against this situation.

The first approach would be to limit polymedication whenever possible. In an elderly population, the identification of drugs with a bad taste could also be a first-line measure. The use of taste sensing technology could aid in the design of new drug formulations with better tastes, but technology cannot replace individual evaluation (12). A questionnaire related to appetite, hunger and sensory perception might not be a reliable tool in a geriatric population, due to the high prevalence of cognitive impairment (13). Due to the huge variability that we observed between participants and between drugs, it appears necessary for dysphagic elderly person to sample each drug in his/her prescription list, in order to identify unacceptable drugs. In case of cognitive troubles, nurse's aides are used to interpret patients' body language for food refusal and this approach would likely be easier than to find alternative solutions for an entire prescription list. Drug tasting could be scheduled among other workshops, organized by family members, dieticians or psychologists, for instance.

Physicians and pharmacists are not always aware of the difficulties encountered by nurses, nurse's aides or family members in the administration of medications. The present study may help promote communication, and caregivers should inform physicians and pharmacists of drug refusal. In some cases, blended food can be considered as a real mistreatment (14). In the present study, the free comments of several participants revealed that the addition of bad-tasting drugs into blended food could be considered as another mistreatment and should be avoided.

In case of drug refusal, physicians and pharmacists might provide a range of alternative solutions. Attention should be focused on the problematic drug, while other medications might be well tolerated. Medical solutions could be: (1) discontinuing the drug, (2) if they are available, the prescription of alternative molecules with a better taste, or (3) the prescription of other dosing formulations (pediatric formulation, powder, liquid, suppository, patch, sustained-release formulation, etc.) (3, 15–19).

Dietary supplements, such as apple sauce vs. jelly (Table 1-4) may help make molecules more palatable. Jam, yogurts or other dietary products may be valuable alternatives. Sugar seems consensual to mask bitterness [20], but a frequent limit is diabetes mellitus. There is also an increased risk of dental caries, particularly with patients who are given polypharmacy and who frequently suffer from drug-induced xerostomia. Zopiclone, for instance, is a hypnotic medicine given at bed-time after oral hygiene care, and evening sugar intake cannot be recommended to dentate patients in such conditions. Other sweeteners or suspending agents are also available to improve drug palatability (21). The nurse's aide participating in the study made the recommendation to concentrate the crushed drugs into one or two spoons of jam, rather than to dilute them in a larger volume. Breakfast milk, porridge, soup, mashed vegetables and sweets should be avoided. The chef recommended chewing white bread or green apple after tasting, instead of drinking water to clean the mouth, because water can increase bitterness.

Finally, since the Prescription Drug User Fee Act and Food and Drug Administration Amendments Act of 2007, it is mandatory for pharmacological companies to test new medicines in clinical assays involving pediatric populations. Consequently, several companies proposed physical alteration to mask bitter taste and improve treatment compliance in children. Current solutions are: granule formulation (17), suppositories/mucoadhesive gels (15), micro- or nanostructures and nanohydrids (19, 22), hot melt extrusion (19), cyclodextrin inclusion alone or combined with lipid coating or ion exchange resin (23, 24). Similar to having these newly developed "children-friendly" drugs, it would be useful to have a strategy dedicated to the elderly population (7–9, 15–18, 25–27).

In conclusion, the taste of some drugs may be unbearable when they are crushed and mixed into food, and caregivers should avoid mixing bad-tasting drugs with other

more palatable drugs. There are wide differences of taste acceptability from one person to another. Thus, during workshops, each patient could taste once separately any single drug in his or her prescription list. In case of drug refusal, caregivers should inform physicians and pharmacists, who in turn should seek medical alternatives (drug discontinuation or substitution). Caregivers could employ alternative food serving or administration conditions. Pharmaceutical companies should also develop specific medicines for the older populations, in parallel with "children-friendly" medicines.

Acknowledgements: The Authors thank Prof Philippe Bahadoran, the medical staff of the Center of Clinical Research (Nice University Hospital) and the 16 volunteers. They thank Dr Dale Rosenbach for manuscript revision (Clinical Instructor & Course Director, Periodontics & Implant Dentistry at Woodhull Medical Center, New York, USA).

Funding sources: Solidages (Nice, France), Institut du bien vieillir Korian (Paris, France) and Nice University Hospital (Nice, France). Sponsors played no role in the study.

Conflict of interest: The authors declare no conflict of interest with the present study.

Ethical Standards: The protocol was approved by the "CPP Sud Méditerranée V" Ethics Committee and registered by Health Authorities under Eudract n° 2013-003461-34.

References

1. Patterson SM, Hughes C, Kerse N, et al. (2012) Interventions to improve the appropriate use of polypharmacy for older people. Cochrane Database Syst Rev 5:CD008165. doi: 10.1002/14651858.CD008165.pub2
2. Sura L, Madhavan A, Carnaby G, Crary MA (2012) Dysphagia in the elderly: management and nutritional considerations. Clin Interv Aging 7:287–298. doi: 10.2147/CIA.S23404
3. (2014) Crushing tablets or opening capsules: many uncertainties, some established dangers. Prescrire Int 23:209–211, 213–214.
4. Utilisation des antisécrétoires gastriques et autres médicaments antiulcéreux dans le Département de Gériatrie des Hôpitaux... - cappinfo26.pdf. http://pharmacie.hug-ge.ch/infomedic/cappinfo/cappinfo26.pdf. Accessed 11 Mar 2015
5. couper,ecraser, ouvrir_finale - Couper_ouvrir_ écraser_mars_2013.pdf. http://www.phel.ch/secure/Pdf/Couper_ouvrir_%20%C3%A9craser_mars_2013.pdf. Accessed 11 Mar 2015
6. Levit A, Nowak S, Peters M, et al. (2014) The bitter pill: clinical drugs that activate the human bitter taste receptor TAS2R14. FASEB J Off Publ Fed Am Soc Exp Biol 28:1181–1197. doi: 10.1096/fj.13-242594
7. Abdulla S, Sagara I (2009) Dispersible formulation of artemether/lumefantrine: specifically developed for infants and young children. Malar J 8 Suppl 1:S7. doi: 10.1186/1475-2875-8-S1-S7
8. Ferrarini A, Bianchetti AA, Fossali EF, et al. (2013) What can we do to make antihypertensive medications taste better for children? Int J Pharm 457:333–336. doi: 10.1016/j.ijpharm.2013.07.054
9. Ali AA, Charoo NA, Abdallah DB (2014) Pediatric drug development: formulation considerations. Drug Dev Ind Pharm 40:1283–1299. doi: 10.3109/03639045.2013.850713
10. Uestuener P, Ferrarini A, Santi M, et al. (2014) Taste acceptability of pulverized brand-name and generic drugs containing amlodipine or candesartan. Int J Pharm 468:196–198. doi: 10.1016/j.ijpharm.2014.04.035
11. Gastalver-Martín C, Alarcón-Payer C, León-Sanz M (2014) Individualized measurement of disease-related malnutrition's costs. Clin Nutr Edinb Scotl. doi: 10.1016/j.clnu.2014.10.005
12. Ikezaki H (2014) [Development of taste sensor for bitterness evaluation of drugs]. Yakugaku Zasshi 134:313–316.
13. Savina C, Donini LM, Anzivino R, et al. (2003) Administering the "AHSP Questionnaire" (appetite, hunger, sensory perception) in a geriatric rehabilitation care. J Nutr Health Aging 7:385–389.
14. Pouyssegur V, Brocker P, Schneider SM, et al. (2015) An innovative solid oral nutritional supplement to fight weight loss and anorexia: open, randomised controlled trial of efficacy in institutionalised, malnourished older adults. Age Ageing 44:245–251. doi: 10.1093/ageing/afu150
15. Jannin V, Lemagnen G, Gueroult P, et al. (2014) Rectal route in the 21st Century to treat children. Adv Drug Deliv Rev 73:34–49. doi: 10.1016/j.addr.2014.05.012
16. Ivanovska V, Rademaker CMA, van Dijk L, Mantel-Teeuwisse AK (2014) Pediatric drug formulations: a review of challenges and progress. Pediatrics 134:361–372. doi: 10.1542/peds.2013-3225
17. Kibleur Y, Dobbelaere D, Barth M, et al. (2014) Results from a Nationwide Cohort Temporary Utilization Authorization (ATU) survey of patients in france treated with Pheburane(®) (Sodium Phenylbutyrate) taste-masked granules. Paediatr Drugs 16:407–415. doi: 10.1007/s40272-014-0081-5
18. Liu F, Ranmal S, Batchelor HK, et al. (2014) Patient-centred pharmaceutical design to improve acceptability of medicines: similarities and differences in paediatric and geriatric populations. Drugs 74:1871–1889. doi: 10.1007/s40265-014-0297-2
19. Kaushik D, Dureja H (2014) Recent patents and patented technology platforms for pharmaceutical taste masking. Recent Pat Drug Deliv Formul 8:37–45.
20. Mennella JA, Reed DR, Mathew PS, et al. (2015) "A spoonful of sugar helps the medicine go down": bitter masking by sucrose among children and adults. Chem Senses 40:17–25. doi: 10.1093/chemse/bju053
21. Wilken MK, Satiroff BA (2012) Pilot study of "miracle fruit" to improve food palatability for patients receiving chemotherapy. Clin J Oncol Nurs 16:E173–177. doi: 10.1188/12.CJON.E173-E177
22. Coupland JN, Hayes JE (2014) Physical approaches to masking bitter taste: lessons from food and pharmaceuticals. Pharm Res 31:2921–2939. doi: 10.1007/s11095-014-1480-6
23. Ge Z, Yang M, Wang Y, et al. (2014) Preparation and evaluation of orally disintegrating tablets of taste masked phencynonate HCl using ion-exchange resin. Drug Dev Ind Pharm. doi: 10.3109/03639045.2014.914529
24. Samprasit W, Akkaramongkolporn P, Ngawhirunpat T, et al. (2014) Formulation and evaluation of meloxicam oral disintegrating tablet with dissolution enhanced by combination of cyclodextrin and ion exchange resins. Drug Dev Ind Pharm 1–11. doi: 10.3109/03639045.2014.922573
25. Milani G, Ragazzi M, Simonetti GD, et al. (2010) Superior palatability of crushed lercanidipine compared with amlodipine among children. Br J Clin Pharmacol 69:204–206. doi: 10.1111/j.1365-2125.2009.03580.x
26. Lucas-Bouwman ME, Roorda RJ, Jansman FG, Brand PL (2001) Crushed prednisolone tablets or oral solution for acute asthma? Arch Dis Child 84:347–348.
27. Schlagenhauf P, Adamcova M, Regep L, et al. (2011) Use of mefloquine in children - a review of dosage, pharmacokinetics and tolerability data. Malar J 10:292. doi: 10.1186/1475-2875-10-292

CHAPITRE III

Thirty drugs frequently prescribed in nursing homes: an *in vitro* screening of the anti-bacterial and anti-*Candida* properties of crushed medications

J. Lamure [a,b], M. Chevalier [b,c] , I. Prêcheur [a,b]

Submitted for publication in

Journal of Medical Microbiology

CHAPITRE III – Avant-propos

Résumé

Les médicaments sont souvent écrasés et mélangés dans une compote ou un laitage, pour pouvoir être pris par les personnes âgées qui ont des troubles de la déglutition ou des troubles du comportement. La Haute Autorité de Santé a publié la liste des médicaments autorisés à être écrasés, car cette pratique peut modifier la pharmacocinétique de certains médicaments, et les rendre inactifs voire toxiques. Il existe aussi un risque direct d'anorexie lié au goût donné aux aliments, mais aucune étude ne l'a évalué.

Enfin, les principes actifs ou l'enrobage des médicaments pourraient avoir un impact sur les bactéries et les *Candida* du biofilm oral, lorsqu'ils sont directement à leur contact. En effet, des micro-organismes endogènes assurent l'hydratation et la viscosité du biofilm oral, et donc une bouche saine et le confort du patient. La pratique des médicaments écrasés pourrait contribuer à expliquer la sécheresse buccale, qui est très fréquente chez les résidents des établissements d'hébergement pour personnes âgées dépendantes (EHPAD). La sécheresse buccale augmente notamment le risque de candidoses orales, de pneumonies d'inhalation, d'anorexie et de dénutrition.

L'**objectif** est de rechercher in vitro si certains médicaments inhibent ou au contraire stimulent la croissance microbienne et risquent d'altérer le biofilm oral

Matériels et Méthodes :

Nous avons testé *in vitro* si les 30 médicaments les plus prescrits en EPADH inhibent ou au contraire stimulent la croissance microbienne. Nous avons testé d'abord leur impact sur les souches de référence (normes AFNOR) et ensuite sur des souches orales (*Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Candida albicans. Streptococcus salivarius,*

Gemella haemolysans). Par la suite les médicaments ont été testés sur des biofilms monoespèces (*Streptococcus salivarius, Candida albicans*).

Résultats :

Seulement huit des trente médicaments testés inhibent la croissance des souches microbiennes : acide acétylsalicylique, amlodipine, alprazolam, miansérine, clopidogrel, citalopram, fluindione et bensérazide levodopa. Ces huit médicaments ont été secondairement testés au contact de biofilms monoespèces (*C. albicans* et *S. salivarius)* en formation ou préformés. Les huit médicaments testés ont eu un impact sur la formation du biofilm de *C. albicans*. Durant la formation du biofilm, la réduction de viabilité varie de 58.4 % à 100 %. Sur un biofilm préformé et après 5 minutes de contact, 4 médicaments (acetylsalicylic acid, amlodipine, citalopram and mianserine) diminuent la viabilité du biofilm de *C. albican*. Six médicaments réduisent aussi la biomasse totale lorsqu'ils sont incubés avec *S. salivarius*. Ces six médicaments ont été plus efficaces que la chlorhexidine, utilisée comme contrôle après un contact de 5 minutes (≥ 25% d'inhibition avec acide acétylsalicylique, amlodipine et alprazolam).

Conclusion :

Huit des 30 médicaments écrasés testés ont eu un impact direct sur les 5 souches bactériennes et sur *C. albicans*. Ces médicaments ont aussi eu un impact sur l'intégrité des biofilms. La question d'un impact *in vivo* est soulevée.

Thirty drugs frequently prescribed in nursing homes: an *in vitro* screening of the anti-bacterial and anti-*Candida* properties of crushed medications

J. Lamure [a,b], M. Chevalier [b,c] , I. Prêcheur [a,b]

[a] Department of Dentistry, Nice University Hospital, Nice, France
[b] Micoralis Laboratory EA7354, Faculty of Dentistry, University of Nice Sophia Antipolis, Nice, France
[c] IP-TPT UMR MD3, Aix-Marseille University, Marseille, France

[*] Corresponding author. Micoralis Laboratory, Faculty of Dentistry, 24 avenue des Diables Bleus, 06357 Nice cedex 4, France. Tel.: +33 4 92 00 11 00.
E-mail address: drjulielamure@gmail.com (J. Lamure)

Keywords: Anorexia, aging, biofilm, medication

Subject Category: Nursing home, elderly, oral biofilm, crushed medication

Word Counts: 4409 words

Conflict of interest: No conflict of interest for any of the three authors

Abstract:

Frail elderly people are often polymedicated and they also frequently suffer from swallowing disorders (dysphagia). As a precaution, these patients are often given blended food and nursing staff is also obliged to crush their medication and to mix drugs into their meals. Crushing drugs raises pharmacological and gustative problems. Besides, crushed drugs may have antimicrobial properties and they may be maintained in prolonged contact with the oral microbial biofilm. Crushing drugs could contribute to misbalance the oral ecosystem and to alter oral health of frail elderly people. The present work aimed to investigate the antimicrobial properties of the 30 most prescribed drugs in nursing homes. Tablets were crushed and capsules were opened in 1 mL of isotonic water. Microbial growth inhibition of *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Streptococcus salivarius, Gemella haemolysans* and *Candida albicans* was screened by the diffusion method on agar plates. Eight drugs inhibited microbial growth. They were secondly tested on *C. albicans* and *S. salivarius* biofilms grown in liquid medium. All the eight drugs tested had an impact on *C. albicans* biofilm formation. During biofilm formation, the reduction of viability ranged from 58.4 % to 100 %. On an already formed biofilm and after only 5 minutes of contact, four drugs (acetylsalicylic acid, amlodipine, citalopram and mianserine) decreased *C. albicans* viability. Six drugs also reduced the total biomass when they were incubated with *S. salivarius*. These six drugs were more efficient than the chlorhexidine used as control after 5 minutes of contact (≥ 25% inhibition with acetylsalicylic acid, amlodipine and alprazolam). In conclusion, eight out of 30 drugs after crushing had a direct impact on five bacterial strains and *C. albicans*. The question of their oral impact *in vivo* is addressed.

Introduction:

Anorexia is a frequent condition in elderly people [1]. In nursing homes and hospital wards it can reach between 20 % to 65 % of this population [2, 3], and up to 85% of long term care residents [4–7].

Besides, many older adults suffer from chronic disease and they are often polymedicated. In nursing homes, they are administered an average of six to eight drugs daily, corresponding to six to 20 tablets or capsules [8]. Over 50% of residents from those institutions are affected by swallowing disorders due to stroke, cancer, Parkinson's disease, Alzheimer's disease, Sjögren's syndrome and to some medications that can cause xerostomia or neuromotor alterations. The resulting dysphagia increases the risk of aspiration pneumonia. The consequent beverage and food refusal can lead to dehydration, anorexia and malnutrition [1, 9]. As a precaution, these patients are often given blended food [10]. Nursing staff is also obliged to crush tablets, to open capsules, and to mix drugs into textured food, frequently made with blenders. Crushing drugs is a common practice in nursing homes [11]. In France, 63% of resident's prescription is crushed [11].

Crushing drugs can induce chemical (e.g. oxidization, acid-basic interaction) and pharmacologic problems (such as with gastro-resistant tablets). Listing of drugs authorized for crushing and consensual recommendations for their administration have been published by several groups of experts [12, 13]. According to recommendations: physicians should limit drug prescription [13], pharmacists should propose alternative formulation such as oral drops whenever possible [10], and nurses should only crush authorized drugs, they should do so separately just before administration and they should mix them into separated food servings [12]. Despite these recommendations, in practice, an observational study in French nursing homes and hospital wards involving 683 patients revealed that 41.5 % of crushed medications were not allowed to be given in this condition [11]. It was also commonly observed that several drugs are crushed together and administered in the same food serving [12].

In a previous interventional study involving 16 healthy volunteers, [14], we showed that the taste of some drugs such as zopiclone, clopidogrel and paracetamol could be unbearable when they were crushed and mixed into food. This feeling was even worst when the medications were crushed and mixed all together as it is commonly done in geriatric wards. The unbearable bitter taste of some crushed drugs could lead to food refusal and contribute to anorexia in polymedicated frail elderly people. Furthermore, in a previous prospective observational study involving 120 polymedicated patients, we observed that antimicrobial mouthwashes could be a risk factor of xerostomia, independently of other risk factors (polymedication, atropinic drugs and/or tobacco smoking) [15].

These observations raised another question: is it possible that, in addition to chemical interactions and taste alterations, some crushed drugs could display intrinsic antimicrobial properties and alter the protective oral microbial biofilm?

The oral biofilm is a three dimensional microbial structure covering host surfaces. In the healthy biofilm, more than 700 species of bacteria have been identified embedded in a exo-polysaccharide matrix [16, 17]. The dynamic balance between host and biofilm creates a commensal protection against opportunistic pathogens [18]. Crushed drugs may be maintained in prolonged contact with the oral microbial biofilm, especially when patients suffer from swallowing disorders. If some active principle have an antimicrobial effect, crushing drugs could contribute to misbalance the oral ecosystem and to alter oral health of frail elderly people. The oral biofilm is also in charge of moisturizing the mouth. In fact, saliva is made of water, electrolytes, proteins from the salivary glands and bacteria. These commensal bacteria contribute to viscosity and hydrating properties of the oral biofilm [19, 20]. Dry mouth is a common symptom of polymedicated patients [9]. Dry mouth can be a direct side effect of atropinic medications or it could be an adverse effect following the contact between medications and the oral biofilm. The aim of this study was to screen *in vitro*, the antimicrobial properties of the 30 most prescribed drugs in nursing homes in France. The null hypothesis

was that crushed medication had no effect on microbial growth, biofilm formation and biofilm elimination.

Materials and methods

Crushed drugs

The 30 drugs tested were selected as the top-list of the drugs prescribed in 2013 in the 596 nursing homes of the Groupe Korian (France). Tablets or capsules with or without crushing authorization were tested [21]. A single tablet was crushed, or a single capsule was opened and then diluted in 1mL of isotonic water. The pH was measured for every drug in solution. The drugs were obtained from the pharmacy of Nice University Hospital, as part of the MELA protocol approved by the local Ethics Committee and registered by Health Authorities under Eudract n° 2013-003461-34 [14].

Microbial strains and culture conditions

Three reference bacterial strains recommended by the Association Française de Normalization (AFNOR) were used to screen antibacterial properties of the drugs: *Escherichia coli* CIP 54.127, *Staphylococcus aureus* CIP 53.154 and *Pseudomonas aeruginosa* CIP A22. These strains were grown aerobically at 37 °C overnight, on Mueller–Hinton agar (bioMérieux, France). Two oral strains were also tested: *Streptococcus salivarius* CIP 102.505 and *Gemella haemolysans* CIP 101.126. They were grown aerobically on 5% sheep's blood agar for 2 days at 37 °C.

A fungal AFNOR reference strain of *Candida albicans* ATCC 10231 was also tested. *C. albicans* was cultivated aerobically on Sabouraud Chloramphenicol agar (bioMérieux, France) for 24 h at 37 °C.

Microbial growth inhibition

Microbial growth inhibition was investigated by the diffusion method with 100 µL of bacterial (10^8 c.f.u.) or fungal (10^6 c.f.u.) inoculum smeared onto agar plates, and 40 µL of crushed drugs solution deposited into pits of 5 mm diameter. Diameter of growth inhibition was measured after 24 h of incubation.

Effect of the drugs on the formation of *S. salivarius* / *C. albicans* biofilms

Bacteria and *C. albicans* biofilms were grown on commercially available pre-sterilized, polystyrene, flat bottomed 96-well microtiter plates (Corning, U.S.A). Biofilms were formed by pipetting standardized cell suspensions into wells: 100 µL of a suspension containing 10^8 cells mL^{-1} in Schaedler broth (bioMérieux, France) for *S. salivarius* and 10^6 cells mL^{-1} in RPMI 1640 (Roswell Park Memorial Institute medium) buffered with MOPS (3-(/N/-morpholino) propanesulfonic acid) [22] for *C. albicans*. In order to determine whether drugs had an effect on biofilm formation, 50 µL of crushed drugs solution were added to *S. salivarius*/*C. albicans* suspensions. Microbial suspensions incubated with isotonic water instead of drugs and biofilm-free wells were included to serve as positive and negative controls, respectively. Plates were incubated for 24 h (*C. albicans*) or 48 h (*S. salivarius*) at 37 °C on an orbital shaker at 100 r.p.m. After biofilm formation, the medium was aspirated. Non-adherent cells were removed by thoroughly washing the biofilms twice with PBS (pH 7.2).

For *S. salivarius*, quantification of the total biofilm biomass was performed by crystal violet staining. Briefly 150 µL of crystal violet (1% v/v) was added into the wells and incubated for 15 min at 37°C. The plates were washed again and air-dried, followed by addition of 200 µL of 95% ethanol and shaking for 5 minutes to suspend intracellular bound crystal violet before measuring optical density at 630 nm [23].

For *C. albicans*, a semiquantitative measure of biofilm formation was obtained using a 2,3-bis(2-methoxy-4-nitro-5-sulfo-phenyl)-2H-tetrazolium-5 carboxanilide (XTT) reduction assay as described previously [24]. Briefly, 100 µL of water were added to each of the prewashed biofilms and into control wells. Then 50 µL volumes of XTT reaction mixture (activation reagent

and XTT reagent) were added according to manufacturer's recommendations (Cell Proliferation kit XTT, AppliChem, Germany). Plates were incubated in the dark for 2 hours at 37 °C. A colorimetric change resulting from XTT reduction and representing a direct correlation of metabolic activity of the biofilm was measured with a microtitre plate reader (ELx800, Biotek Instruments, U.S.A) at 490 nm. An inhibitory percentage was calculated by the following formula: [(control−treatment)/control] ×100. All experiments were done in triplicate on three independent assays. Isotonic water was used as negative control. A brand mouthwash containing 0.12% chlorhexidine was used as a Positive Control.

Effect of drugs on pre-formed *S. salivarius*/ *C. albicans* biofilms

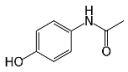
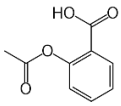
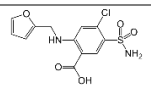
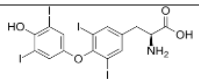
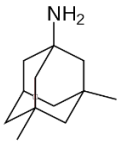
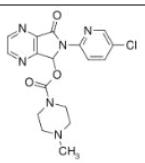
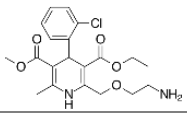
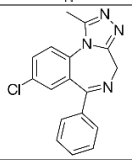
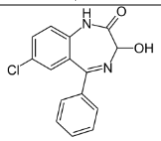
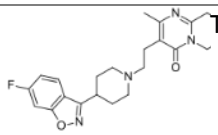
Biofilms were obtained as described before. After 24 h of incubation, the medium was aspirated and non-adherent cells were removed by thoroughly washing the biofilms with PBS. Then, 100 µL of crushed drugs solution were added into wells. Isotonic water and chlorhexidine mouthwash were used as negative and positive control. Microtitre plates where incubated for 5 min on an orbital shaker at 100 r.p.m. Biofilms were then washed and XTT reaction was measured as described before.

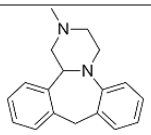
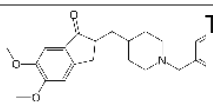
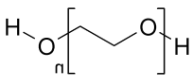
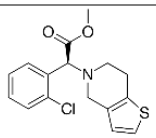
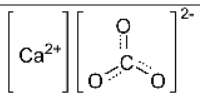
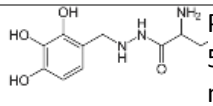
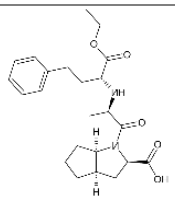
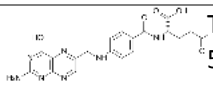
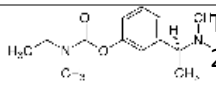
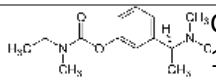
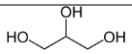
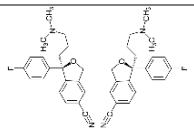
All the tests were done in triplicate, in three separate occasions

Results

Medications and pH

The 30 drugs tested are listed in descending order of prescription rate in Table 1. In solution, their pH ranged from 5 to 8.5.

Drugs INN (Laboratory)	Formula	Formulation	Main indication	pH in isotonic water	Authorized to be crushed
Paracetamol (Sanofi-Aventis)		Capsule 500 mg	Analgesic	7.5	Crushed
Acetylsalicylic acid (Sanofi Aventis)		Powder 100 mg	Analgesic, Antiplatelet	6	No
Furosemide (Sanofi Aventis)		Tablet 20 mg	Anti hypertensive, loop diuretic	6	Crushed
Levothyroxine sodium (Merck)		Tablet 25 µg	Thyroid hormone	6	Crushed
Memantine (Lundbeck)		Tablet 10 mg	Alzheimer's disease	6	Crushed
Potassium chloride (E508) (UCB Pharma)	K-Cl	Capsule 600 mg	Hypocalcemia	6	No
Zopiclone (Arrow)		Tablet 7.5 mg	Hypnotic, benzodiazepine	6.5	Crushed
Amlodipine (Pfizer)		Capsule 5 mg	Antihypertensive , calcium channel blockers.	6,5	No
Alprazolam (Mylan)		Tablet 0.25 mg	Anxiolytic benzodiazepine	6,5	Crushed
Oxazepam (Biodim)		Tablet 10 mg	Anxiolytic, benzodiazepine	6	Crushed
Risperidone (Janssen Cilag)		Tablet 1 mg	Neuroleptic	6	No

Mianserin (Arrow)		Tablet 10 mg	Antidepressant, tetracyclic	6	No
Donepezil (Mylan)		Tablet 5 mg	Acetylcholinesterase inhibitor , Alzheimer's disease	6	Crushed
Macrogol 4000 (Bayer)		Powder 5.9 g	Laxative	8,5	No
Clopidogrel (Sanofi Pharma)		Tablet 75 mg	Anti-platelet	5	Crushed
Calcium Vitamin D3 (Sandoz)		Tablet 100 mg	Against osteoporosis	8,5	No
Benserazide; Levodopa (Roche)		Powder 50 mg/ 12.5 mg	Co-beneldopa, Parkinson's disease	6,5	No
Ramipril (Sanofi Aventis)		Tablet 1.25 mg	Antihypertensive, angiotensin converting enzyme inhibitor	6	Crushed
Folic acid (C.C.D)		Tablet 5 mg	B Vitamin	6	Crushed
Amiodarone (Arrow)		Tablet 200 mg	Antiarhythmic agent	6,5	Crushed
Rivastigmine (Novartis)		Capsule 1.5 mg	cholinergic agent, Alzheimer's disease	6	No
Glycerol (E422);Vaseline (Cooper)		Suppository	lubricant	Not tested	No
Citalopram (Lundbeck)		Tablet 20 mg	Antidepressant, serotonin reuptake inhibitor	7,5	Crushed

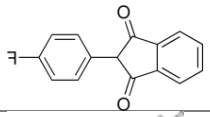
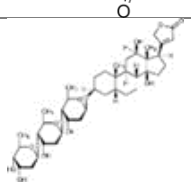
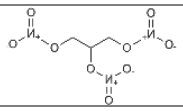
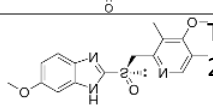
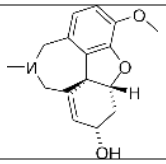
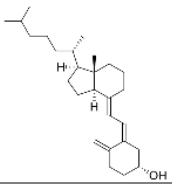
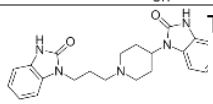
Fluindione (Merck Serono)		Tablet 20 mg	Vtamin K antagonist	5	Crushed
Digoxin (Teofarma)		Tablet 0.25 mg	Cardiac glycoside	6	Crushed
Trinitrine (Tonipharm)		Tablet 0.15 mg	Angina	6	No
Esomeprazole (Astra Zeneka)		Tablet 20 mg	Proton pump inhibitor, inhibits gastric acid secretion	6	No
Galantamine (Janssen-Cilag)		Capsule 24 mg	Alzheimer's disease	6	Crushed
Cholecalciferol (Crinex)		Single-dose vial 2.5 mg	D3 Vitamin deficiency	6	No
Domperidone (Arrow)		Tablet 10 mg	Antagonist of the dopamine D2 and D3 receptors, against nausea	6.5	No

Table 1. The 30 most prescribed drugs in nursing homes (in descending order of prescription rate) with their pharmacological features. INN: international nonproprietary name.

Microbial growth inhibition

A total of eight drugs out of 30 displayed antibacterial and/or antifungal properties. Each drug displayed a different spectrum of inhibition. Very active drugs were amlodipine, citalopram, clopidogrel and benserazide levodopa. Moderately active drugs were acetylsalicylic acid and mianserine. Less active ones were fluindione and alprazolam. Results are detailed in Table 2.

	E. coli CIP 54.127	*P. aeruginosa* CIP A22	*S. aureus* CIP 53.154	*G. haemolysans* CIP 101.126	*S. salivarius* CIP 102.505	*C. albicans* IP 48.72
Acetylsalicylic acid	0 ± 0	0 ± 0	9 ± 0	14.5 ± 0.7	0 ± 0	0 ± 0
Amlodipine	13.5 ± 0.7	8.75 ± 0.3	18 ± 4.2	23 ± 5.6	13.5 ± 0.7	10 ± 2.8
Alprazolam	0 ± 0	0 ± 0	10± 1.4	0 ± 0	0 ± 0	0 ± 0
Mianserine	9.5 ± 0.7	0 ± 0	8.75 ± 1.8	8 ± 0	7 ± 0	8.5 ± 0.7
Clopidogrel	7 ± 0	9.5 ± 2.1	10 ± 4.2	6.25 ± 0.3	12.5 ± 2.1	0 ± 0
Citalopram	16 ± 0	6 ± 0	11 ± 0	12.5 ± 0.7	9.5 ± 0.7	10.5 ± 0.7
Fluindione	0 ± 0	0 ± 0	16.5 ± 7.8	9 ± 4.2	0 ± 0	0 ± 0
Benserazide Levodopa	13.5 ± 0.7	18 ± 0	34 ± 5.6	34 ± 0	0 ± 0	0 ± 0
Negative Control: Isotonic water	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Positive Control: Chlorhexidine	19.5 ± 0.7	12.25 ± 0.3	31 ± 1.4	18 ± 0	15 ± 1.4	12.5 ± 0.7

Table 2: Diameter of microbial growth inhibition (mm) of bacterial (10^8 c.f.u.) or fungal (10^6 c.f.u.) inoculum smeared onto agar plates, and 40 µL of crushed drugs solution deposited into pits of 5 mm diameter. Diameter of growth inhibition was measured after 24 h of incubation.

In addition to antibacterial properties, 10 out of 30 drugs tested also displayed hemolytic properties around the pits on 5% sheep's blood agar plates. The 10 drugs were, with decreasing hemolytic properties: galantamine 26 ± 1.4 mm; benserazide levodopa 17.5 ± 3.5 mm, clopidogrel 12.5 ± 2.1 mm ; amlodipine 11 ± 0 mm; alprazolam 9.5 ± 0.7 mm; citalopram 8 ± 2.8 mm; domperidone 8 ± 0 mm; mianserine 7 ± 0 mm; amiodarone 6 ± 0 mm; potassium chloride 6 ± 0 mm (Positive Control: chlorhexidine 10 ± 0 mm).

Among these active principles, four displayed hemolytic activity but no inhibition of bacterial or fungal growth (amiodarone, domperidone, potassium chloride, galantamine).

Streptococcus salivarius biofilm

The eight drugs which displayed antibacterial and/or antifungal properties onto blood agar plates where secondly screened in order to test their anti-biofilm properties. Microbial suspensions were grown into microtiter plate wells, forming a biofilm adherent to polystyrene.

Effect of drugs on the formation of S. salivarius biofilms

The percentage of reduction in *S. salivarius* biofilm formation was: alprazolam 95.9 ± 3.6%; acetylsalicylic acid 78.8 ± 4.5%; amlodipine 75.9 ± 6.5%; mianserine 59.1 ± 11.3%; citalopram 50.4 ± 15.8%; fluindione 67.0 ± 13.1% and chlorhexidine 45.8 ± 25.7%. No reduction of the biofilm was observed with clopidogrel or benserazide levodopa.

Effect of drugs on pre-formed S. salivarius biofilm

Exposure of pre-formed 48 h *S. salivarius* biofilm to drugs for 5 min resulted in reduction in viability compared to control biofilms. The percentage of reduction observed was: chlorhexidine 39.7 ± 1.7%; acetylsalicylic acid 24.8 ± 15.9%; alprazolam 24.8 ± 9.0% and amlodipine 24.5 ± 22.5%. No biofilm reduction was observed with benserazide levodopa, citalopram, clopidogrel, mianserine and fluindione.

Six drugs among the eight tested reduced the total biomass when they were incubated with *S. salivarius*. These six drugs were more efficient to reduce the biomass than chlorhexidine used as Positive Control. After 5 min of contact, acetylsalicylic acid, amlodipine and alprazolam reduced the total mass of bacteria by approximately 25%.

Candida albicans biofilm

Effect of crushed drugs on the formation of C. albicans biofilm

C. albicans ATCC 10231 produced a significant biofilm (OD 490: 1.17 ± 0.31). Negative Control was attributed 100% viability of *C albicans* in biofilm. The percentage of reduction in biofilm formation was, in decreasing order of efficacy : acetylsalicylic acid 101.6 ±13.2 %;

amlodipine 101.3 ± 12.9 %; alprazolam 101.2 ± 13.3%; miansérine 94.8 ± 11.6%; clopidogrel, 68.6 ± 21.1%; citalopram 58.4 ± 18.6%; fluindione 86.8 ± 15.7% and chlorhexidine (Positive Control) 9.6 ± 0.49%.

All the drugs tested had an impact on the biofilm formation by *C. albicans*. The reduction of *Candida* viability was between 58.4 ± 18.6% and 101.6 ± 13.2%.

Effect of crushed drugs on pre-formed C. albicans biofilm

Exposure of pre-formed 18 h *C. albicans* biofilms to crushed drugs for 5 min resulted in reduction in viability compared to Control biofilm for four drugs. The percentage of reduction observed, in decreasing order of efficacy, was: amlodipine 73.5 ± 6.8%; citalopram 31.2 ± 9.9%; acetylsalicylic acid 23.4 ± 6.6%; mianserine 11.6 ± 8.9% and chlorhexidine (Positive Control) 95,8% ± 0,55. No reduction of the biofilm was observed with alprazolam, clopidogrel or fluindione.

Benserazide levodopa formed deposits at the bottom of wells and it was impossible to measure optic density with colorimetric methods.

Results of biofilm inhibition are summarized in Table 3. Crushed medications either had an inhibiting effect (+) or no effect (0) on microbial growth and/or biofilm formation/destruction. None of the medications tested increased microbial growth or biofilm formation.

	S. salivarius			*C. albicans*		
	Growth inhibition	**Inhibition of biofilm formation**	**Reduction of a pre-formed biofilm**	**Growth inhibition**	**Inhibition of biofilm formation**	**Destruction of a pre-formed biofilm**
Acetylsalicylic acid	0	+	+	0	+	+
Alprazolam [a]	0	+	+	0	+	0
Amlodipine	+	+	+	+	+	+
Bensarezide levodopa	0	0	0	0	Impossible to read	Impossible to read
Chlorhexidine (Positive Control)	+	+	+	+	+	+
Citalopram [a]	+	+	0	+	+	+
Clopidogrel [a]	+	0	0	0	+	0
Fluindione [a]	0	+	0	0	+	0
Mianserine	+	+	0	+	+	+

Table 3: Effect of medications on microbial growth, biofilm formation and pre-formed biofilm destruction after a contact of 5 min. (0): no effect; (+): inhibiting effect; [a] Crushed medications

Discussion

In our knowledge, this is the first time that crushed medications have been screened for their antimicrobial properties. We tested *in vitro* the antimicrobial properties of the 30 most prescribed drugs in nursing homes, either they were authorized or not to be crushed according to the French Health Authority [21]. Indeed, in practice, these recommendations are not always followed by medical staff [11].

A total of eight drugs out of 30 displayed antibacterial properties in liquid cultures: acetylsalicylic acid, amlodipine, alprazolam, mianserine, clopidogrel, citalopram, fluindione and benserazide levodopa. We could not find chemical similarities with antibiotic or antifungal molecules to explain these results. We actually used drugs under their commercial formulation, as they are used in nursing homes, and not the purified active principles. It is thus possible that some excipients contained in these brand formulations, or their pH, had an impact on the microbial flora.

Regarding *S. salivarius* strain; acetylsalicylic acid, alprazolam and fluindione had no antibacterial properties onto agar plates. Nevertheless, they inhibited *S. salivarius* biofilm

formation. It means that they had a negative effect on the tri-dimensional structure formation of the biofilm. Furthermore, acetylsalicylic acid and alprazolam had also the ability to destroy the structure of a pre-formed *S. salivarius* biofilm. These results suggest that some crushed medications could inhibit the structure of a biofilm even if they don't have direct antibacterial properties.

We actually had some issues with the coating of some drugs. In touch with the medium we observed an immediate change of color with fluindione which gave an orange shade, and with benserazide levodopa which gave a black shade. Furthermore, the latter formed deposits at the bottom of wells that rendered colorimetric methods impossible.

Seven drugs out of the eight tested (we couldn't screen the effect of benserazide levodopa on biofilms) had an impact on the formation of biofilm by *C. albicans,* despite the fact that five of them did not display antifungal properties in liquid culture: acetylsalicylic acid, alprazolam, clopidogrel, fluindione and benserazide levodopa. Exposure of pre-formed 18 h-*C. albicans* biofilms to drugs for 5 minutes resulted in reduction in viability, compared to control biofilm, for four drugs: amlodipine, citalopram, acetylsalicylic acid and mianserine. These results suggest that some crushed medications could inhibit the tri-dimensional structure of a *Candida* biofilm even if they don't have direct antifungal properties.

In the absence of similar studies, we couldn't compare these results with others from the literature on crushed medications.

We found that eight drugs had an inhibitory effect on the growth of AFNOR reference microbial species, as well as two oral endogenous bacterial species. This unexpected property could have an impact on commensal flora. Chlorhexidine was used as a Positive Control because it is an antiseptic mouth rinse commonly used as a clinical reference. In this study, some medications were as efficient than chlorhexidine to inhibit microbial growth. Chlorhexidine rinse, on a daily use has an impact the oral flora and increases xerostomia [15]. Dry mouth is a condition which can lead to anorexia and malnutrition [1,25]. We already found in a previous study that some medication crushed into food could alter the taste, which would increase the risk of food refusal [14].

Further investigations are needed with other microbial strains and mature biofilm. *In vivo* studies would help to study the modification of the oral biofilm induced by crushed medications. Furthermore, frail elderly poeple are often polymedicated; the entire crushed prescription is mixed into their meal and can stay in their mouth when they are suffering from dysphagia. We only studied the impact on medication one by one, but it would be interesting to study a mix of medications.

According to these preliminary results, caregivers should avoid crushing these eight drugs into food, especially alprazolam, clopidogrel, citalopram and fluindione which are authorized to be crushed by the French Health Authority. Furthermore, pharmaceutical companies should also develop specific medicines for the older populations, in parallel with “children-friendly” medicines [26–35] to avoid as much as possible crushing medication.

References

1. Wysokiński A, Sobów T, Kłoszewska I, Kostka T (2015) Mechanisms of the anorexia of aging-a review. Age Dordr Neth 37:9821. doi: 10.1007/s11357-015-9821-x

2. Donini LM, Dominguez LJ, Barbagallo M, et al. (2011) Senile anorexia in different geriatric settings in Italy. J Nutr Health Aging 15:775–781.

3. Donini LM, Poggiogalle E, Piredda M, et al. (2013) Anorexia and eating patterns in the elderly. PloS One 8:e63539. doi: 10.1371/journal.pone.0063539

4. Ahmed T, Haboubi N (2010) Assessment and management of nutrition in older people and its importance to health. Clin Interv Aging 5:207–216.

5. Kerstetter JE, Holthausen BA, Fitz PA (1992) Malnutrition in the institutionalized older adult. J Am Diet Assoc 92:1109–1116.

6. Morley JE (2012) Anorexia of aging: a true geriatric syndrome. J Nutr Health Aging 16:422–425.

7. NHANES - NHANES III. http://www.cdc.gov/nchs/nhanes/nh3data.htm. Accessed 1 Nov 2015

8. Patterson SM, Cadogan CA, Kerse N, et al. (2014) Interventions to improve the appropriate use of polypharmacy for older people. Cochrane Database Syst Rev 10:CD008165. doi: 10.1002/14651858.CD008165.pub3

9. Boczko F (2006) Patients' awareness of symptoms of dysphagia. J Am Med Dir Assoc 7:587–590. doi: 10.1016/j.jamda.2006.08.002

10. Sura L, Madhavan A, Carnaby G, Crary MA (2012) Dysphagia in the elderly: management and nutritional considerations. Clin Interv Aging 7:287–298. doi: 10.2147/CIA.S23404

11. Caussin M, Mourier W, Philippe S, et al. (2012) [Crushing drugs in geriatric units: an "handicraft" practice with frequent errors which imposed recommendations]. Rev Médecine Interne Fondée Par Société Natl Francaise Médecine Interne 33:546–551. doi: 10.1016/j.revmed.2012.05.014

12. (2014) Crushing tablets or opening capsules: many uncertainties, some established dangers. Prescrire Int 23:209–211, 213–214.

13. Utilisation des antisécrétoires gastriques et autres médicaments antiulcéreux dans le Département de Gériatrie des Hôpitaux... - cappinfo26.pdf. http://pharmacie.hug-ge.ch/infomedic/cappinfo/cappinfo26.pdf. Accessed 11 Mar 2015

14. TASTE OF TEN DRUGS FREQUENTLY PRESCRIBED IN NURSING HOMES CRUSHED AND MIXED IN FOOD: OBSERVATIONAL STUDY IN 16 HEALTHY VOLUNTEERS • The Journal of Nursing Home Research. http://www.jnursinghomeresearch.com/483-taste-of-ten-drugs-frequently-prescribed-in-nursing-homes-crushed-and-mixed-in-food-observational-study-in-16-healthy-volunteers.html. Accessed 23 Oct 2015

15. Chevalier M, Sakarovitch C, Precheur I, et al. (2015) Antiseptic mouthwashes could worsen xerostomia in patients taking polypharmacy. Acta Odontol Scand 73:267–273. doi: 10.3109/00016357.2014.923108

16. Paster BJ, Olsen I, Aas JA, Dewhirst FE (2006) The breadth of bacterial diversity in the human periodontal pocket and other oral sites. Periodontol 2000 42:80–87. doi: 10.1111/j.1600-0757.2006.00174.x

17. Reese S, Guggenheim B (2007) A novel TEM contrasting technique for extracellular polysaccharides in in vitro biofilms. Microsc Res Tech 70:816–822. doi: 10.1002/jemt.20471

18. Darveau RP (2010) Periodontitis: a polymicrobial disruption of host homeostasis. Nat Rev Microbiol 8:481–490. doi: 10.1038/nrmicro2337

19. Lacoste-Ferré M-H, Hermabessière S, Jézéquel F, Rolland Y (2013) [Oral ecosystem in elderly people]. Gériatrie Psychol Neuropsychiatr Vieil 11:144–150. doi: 10.1684/pnv.2013.0401

20. Preza D, Olsen I, Willumsen T, et al. (2009) Diversity and site-specificity of the oral microflora in the elderly. Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol 28:1033–1040. doi: 10.1007/s10096-009-0743-3

21. Guide ADM - BOITE_LISTE_NON_SECABLES.pdf.

22. Nett JE, Cain MT, Crawford K, Andes DR (2011) Optimizing a Candida Biofilm Microtiter Plate Model for Measurement of Antifungal Susceptibility by Tetrazolium Salt Assay. J Clin Microbiol 49:1426–1433. doi: 10.1128/JCM.02273-10

23. Krishnamurthy A, Kyd J (2014) The roles of epithelial cell contact, respiratory bacterial interactions and phosphorylcholine in promoting biofilm formation by Streptococcus pneumoniae and nontypeable Haemophilus influenzae. Microbes Infect. doi: 10.1016/j.micinf.2014.06.008

24. Chevalier M, Medioni E, Prêcheur I (2012) Inhibition of Candida albicans yeast-hyphal transition and biofilm formation by Solidago virgaurea water extracts. J Med Microbiol 61:1016–1022. doi: 10.1099/jmm.0.041699-0

25. Morley JE (2013) Pathophysiology of the anorexia of aging. Curr Opin Clin Nutr Metab Care 16:27–32. doi: 10.1097/MCO.0b013e328359efd7

26. Milani G, Ragazzi M, Simonetti GD, et al. (2010) Superior palatability of crushed lercanidipine compared with amlodipine among children. Br J Clin Pharmacol 69:204–206. doi: 10.1111/j.1365-2125.2009.03580.x

27. Lucas-Bouwman ME, Roorda RJ, Jansman FG, Brand PL (2001) Crushed prednisolone tablets or oral solution for acute asthma? Arch Dis Child 84:347–348.

28. Schlagenhauf P, Adamcova M, Regep L, et al. (2011) Use of mefloquine in children - a review of dosage, pharmacokinetics and tolerability data. Malar J 10:292. doi: 10.1186/1475-2875-10-292

29. Abdulla S, Sagara I (2009) Dispersible formulation of artemether/lumefantrine: specifically developed for infants and young children. Malar J 8 Suppl 1:S7. doi: 10.1186/1475-2875-8-S1-S7

30. Ferrarini A, Bianchetti AA, Fossali EF, et al. (2013) What can we do to make antihypertensive medications taste better for children? Int J Pharm 457:333–336. doi: 10.1016/j.ijpharm.2013.07.054

31. Ali AA, Charoo NA, Abdallah DB (2014) Pediatric drug development: formulation considerations. Drug Dev Ind Pharm 40:1283–1299. doi: 10.3109/03639045.2013.850713

32. Jannin V, Lemagnen G, Gueroult P, et al. (2014) Rectal route in the 21st Century to treat children. Adv Drug Deliv Rev 73:34–49. doi: 10.1016/j.addr.2014.05.012

33. Ivanovska V, Rademaker CMA, van Dijk L, Mantel-Teeuwisse AK (2014) Pediatric drug formulations: a review of challenges and progress. Pediatrics 134:361–372. doi: 10.1542/peds.2013-3225

34. Kibleur Y, Dobbelaere D, Barth M, et al. (2014) Results from a Nationwide Cohort Temporary Utilization Authorization (ATU) survey of patients in france treated with Pheburane(®) (Sodium Phenylbutyrate) taste-masked granules. Paediatr Drugs 16:407–415. doi: 10.1007/s40272-014-0081-5

35. Liu F, Ranmal S, Batchelor HK, et al. (2014) Patient-centred pharmaceutical design to improve acceptability of medicines: similarities and differences in paediatric and geriatric populations. Drugs 74:1871–1889. doi: 10.1007/s40265-014-0297-2

CONCLUSIONS

Nous avons montré dans ce travail que, chez les patients hospitalisés et polymédiqués, une utilisation prolongée (supérieure à deux semaines) des bains de bouche antiseptiques était indépendamment associée à la sécheresse buccale. Cette étude nous a incités à étudier l'impact des médicaments écrasés sur le biofilm oral (*in vitro*) et sur la malnutrition (*in vivo*).

In vivo, l'étude clinique organisée comme une dégustation a permis de mettre en évidence que certains médicaments pouvaient donner un mauvais goût aux aliments. Certains médicaments (zopiclone, clopidogrel, paracétamol) et le mélange de médicaments se sont avérés exécrables pour la plupart des goûteurs.

In vitro, nous avons trouvé que huit médicaments écrasés parmi les trente les plus prescrits en EPADH inhibaient la croissance bactérienne : acide acétylsalicylique, amlodipine, alprazolam, miansérine, clopidogrel, citalopram, fluindione et bensérazide levodopa. Quatre d'entre eux présentaient aussi une activité antifongique (amlodipine, mianserine, citalopram et bensérazide lévodopa). Ces huit médicaments ont diminué ou empêché la formation d'un biofilm de *C. albicans*. Lorsqu'un biofilm préformé (18 h de culture) de *C. albicans* était exposé pendant cinq minutes à quatre médicaments (amlodipine, citalopram, acide acétylsalicylique et miansérine) nous avons observé une diminution de sa viabilité. Aucune réduction du biofilm n'a été observée avec alprazolam, clopidogrel, fluindione et chlorhexidine (contrôle positif). Une réduction de la formation d'un biofilm de *S. salivarius* a été observée au contact de six médicaments (acide acétylsalicylique, amlodipine, alprazolam, miansérine, citalopram, fluindione et chlorexhidine). Aucune réduction du biofilm n'a été observée avec clopidogrel et bensérazide lévodopa. Lorsque qu'un biofilm préformé (48 h) de *S. salivarius* est exposé pendant cinq minutes à trois médicaments (acide acétylsalicylique, alprazolam, amlodipine et chlorexhidine,) nous avons observé une diminution de sa viabilité. Aucune réduction du biofilm n'a été observée avec bensérazide levodopa, citalopram, clopidogrel, miansérine et fluindione.

Ces résultats nécessitent des travaux complémentaires, mais ils tendent à montrer que les médicaments écrasés ont un impact négatif à la fois sur le goût et sur le biofilm oral. Ainsi, chez les

personnes âgées souffrant de troubles de la déglutition, la pratique des médicaments écrasés contribuerait à aggraver la sécheresse buccale, la diminution de l'appétit (anorexie) et la malnutrition. L'administration des médicaments sous forme écrasée diminuerait ainsi la qualité de vie des personnes âgées, surtout celles qui prennent beaucoup de médicaments.

L'objectif final de ce travail serait d'améliorer les protocoles de distribution des médicaments en EHPAD et à domicile, et idéalement de trouver ou de proposer des formes galéniques gériatriques, comme en pédiatrie. Ce travail pourrait aussi contribuer à encourager la politique de réduction des prescriptions médicamenteuses.

REFERENCES BIBLIOGRAPHIQUES

1. Insee - Population - Population par âge. http://www.insee.fr/fr/themes/document.asp?ref_id=T12F032. Accessed 26 Oct 2015

2. Sura L, Madhavan A, Carnaby G, Crary MA (2012) Dysphagia in the elderly: management and nutritional considerations. Clin Interv Aging 7:287–298. doi: 10.2147/CIA.S23404

3. Caussin M, Mourier W, Philippe S, et al. (2012) [Crushing drugs in geriatric units: an "handicraft" practice with frequent errors which imposed recommendations]. Rev Médecine Interne Fondée Par Société Natl Francaise Médecine Interne 33:546–551. doi: 10.1016/j.revmed.2012.05.014

4. Guide ADM - BOITE_LISTE_NON_SECABLES.pdf.

5. Haute Autorité de Santé - Stratégie de prise en charge en cas de dénutrition protéino-énergétique chez la personne âgée. http://www.has-sante.fr/portail/jcms/r_1495743/fr/strategie-de-prise-en-charge-en-cas-de-denutrition-proteino-energetique-chez-la-personne-agee. Accessed 7 Nov 2015

6. Haute Autorité de Santé - Diagnostic et prise en charge de la maladie d'Alzheimer et des maladies apparentées. http://www.has-sante.fr/portail/jcms/c_668822/fr/diagnostic-et-prise-en-charge-de-la-maladie-d-alzheimer-et-des-maladies-apparentees. Accessed 7 Nov 2015

7. Suzuki K, Nomura T, Sakurai M, et al. (2005) Relationship between number of present teeth and nutritional intake in institutionalized elderly. Bull Tokyo Dent Coll 46:135–143.

8. Morley JE (2003) Anorexia and weight loss in older persons. J Gerontol A Biol Sci Med Sci 58:131–137.

9. Morley JE (2012) Anorexia of aging: a true geriatric syndrome. J Nutr Health Aging 16:422–425.

10. Bartali B, Salvini S, Turrini A, et al. (2003) Age and disability affect dietary intake. J Nutr 133:2868–2873.

11. Le gout de .....vieillir .... - Memoire de Philippe Briard - Le gout de .....vieillir .... - Memoire de Philippe Briard.pdf.

12. Paster BJ, Olsen I, Aas JA, Dewhirst FE (2006) The breadth of bacterial diversity in the human periodontal pocket and other oral sites. Periodontol 2000 42:80–87. doi: 10.1111/j.1600-0757.2006.00174.x

13. Peyyala R, Ebersole JL (2013) Multispecies biofilms and host responses: "discriminating the trees from the forest." Cytokine 61:15–25. doi: 10.1016/j.cyto.2012.10.006

14. Zijnge V, van Leeuwen MBM, Degener JE, et al. (2010) Oral biofilm architecture on natural teeth. PloS One 5:e9321. doi: 10.1371/journal.pone.0009321

15. Wood SR, Kirkham J, Marsh PD, et al. (2000) Architecture of intact natural human plaque biofilms studied by confocal laser scanning microscopy. J Dent Res 79:21–27.

16. Reese S, Guggenheim B (2007) A novel TEM contrasting technique for extracellular polysaccharides in in vitro biofilms. Microsc Res Tech 70:816–822. doi: 10.1002/jemt.20471

17. Albandar JM, Brunelle JA, Kingman A (1999) Destructive periodontal disease in adults 30 years of age and older in the United States, 1988-1994. J Periodontol 70:13–29. doi: 10.1902/jop.1999.70.1.13

18. Aas JA, Paster BJ, Stokes LN, et al. (2005) Defining the normal bacterial flora of the oral cavity. J Clin Microbiol 43:5721–5732. doi: 10.1128/JCM.43.11.5721-5732.2005

19. Segata N, Haake SK, Mannon P, et al. (2012) Composition of the adult digestive tract bacterial microbiome based on seven mouth surfaces, tonsils, throat and stool samples. Genome Biol 13:R42. doi: 10.1186/gb-2012-13-6-r42

20. Furness S, Bryan G, McMillan R, et al. (2013) Interventions for the management of dry mouth: non-pharmacological interventions. Cochrane Database Syst Rev 9:CD009603. doi: 10.1002/14651858.CD009603.pub3

Je dédie cette thèse…

A Marlène Chevalier : Je n'aurai jamais réussi ce travail sans toi. Je te remercie pour ton aide, tes compétences, ta bonne humeur. Tu es le pilier de ce laboratoire.

A mes parents,

A mes grands-parents,

A Maxime et Laure, mon frère et ma sœur, et aussi Charlotte, Louise et Victoire,

A Adrien,

Au service de parodontologie :

Au Dr Charbit qui m'a encouragé à me lancer dans cette aventure de laboratoire. Je vous remercie également pour votre soutien et votre confiance durant mon assistanat.

Je remercie également le Dr Vincent. Séverine tu as les épaules d'une chef ! Merci pour ton professionnalisme, ta confiance, tes compétences et ton amitié.

Au Laboratoire Micoralis et à mes co-doctorants,

Aux Cabinet de Beausoleil et de Sophia-Antipolis: merci pour votre professionnalisme et votre bonne humeur ; je suis très fière d'être parmi vous. Je vous remercie de m'avoir fait confiance et de me laisser faire ce que j'aime.